AN INVESTIGATION OF THE COGNITIVE EFFECTS OF BIFRONTAL ELECTROCONVULSIVE THERAPY IN THE TREATMENT OF SEVERE DEPRESSION

by

Mikala Lee Saccoman

A dissertation submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Educational Psychology

The University of Utah

August 2011

The University of Utah Graduate School

STATEMENT OF DISSERTATION APPROVAL

The dissertation of **Mikala Lee Saccoman**

has been approved by the following supervisory committee members:

Elaine Clark	, Chair	**3/31/11** Date Approved
Howard Weeks	, Member	**3/31/11** Date Approved
Michael Gardner	, Member	**3/31/11** Date Approved
Lowry Bushnell	, Member	**3/31/11** Date Approved
Janiece Pompa	, Member	**3/31/11** Date Approved

and by **Elaine Clark** , Chair of the Department of **Educational Psychology**

and by Charles A. Wight, Dean of The Graduate School.

ABSTRACT

Although many researchers have examined the effects of electroconvulsive therapy (ECT) on memory and cognition, few investigators have studied the neurocognitive effects of bifrontal electrode placement in ECT treatment. The current study was designed to examine the clinical efficacy and neurocognitive effects of bifrontal ECT. Participants included 17 adults between the ages of 23 and 62 years of age, all of whom had been diagnosed with unipolar or bipolar depression and met hospital criteria for ECT treatment, that is, had failed other treatment efforts. Recruitment of participants took place between 2009 and 2010 at a university-based psychiatric hospital. Following consent to participate and assurance that recruits met study criteria, a psychiatric interview was conducted and psychological/neuropsychological tests were administered. The tests were selected for the purpose of quantifying depressive symptoms and cognitive skills thought to be affected by ECT (anterograde and retrograde memory, executive functions, and processing speed).

Results of the study demonstrated that bifrontal ECT can be an effective treatment of depression in that 88% of participants showed reduced depressive symptoms immediately after ECT treatment and 77% of these initial remitters continued to show response to treatment 1 month later. Although data also

showed that the participants had posttreatment problems with retrograde amnesia which had not resolved by follow-up 1 month later, and had impaired verbal fluency immediately posttreatment which remitted by follow-up, there were no indications that the ECT treatment caused anterograde memory problems or other nonmemory cognitive problems. Specifically data showed no ill effects of bifrontal ECT on processing speed and executive functions (inhibition, motor planning and response, sequencing, and cognitive flexibility). Without a control group or randomized assignment to treatment, no firm conclusions can be drawn from the current findings; however, the findings are important in that they suggest that bifrontal ECT treatment is as effective in addressing treatment-resistant depression as other ECT methods which entail electrode placements that may produce greater and more persistent cognitive side effects, including bitemporal ECT.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Figure Page

ACKNOWLEDGMENTS

I am especially grateful to Howard Weeks, M.D. whose unrelenting dedication and support made this project possible, and Elaine Clark, Ph.D., for devoting much of her time and expertise to assist and guide me through this process. Further, I thank Michael Gardner, Ph.D., Lowry Bushnell, M.D., and Janiece Pompa, Ph.D. for their generous support and guidance.

I express my sincerest gratitude to the participants in this study who gave their time and energy to complete testing amidst difficult times in their lives.

I wish to acknowledge Tony Crespi, ED.D., my master's program advisor and dear friend, who encouraged me to pursue doctoral studies since the day we met and believed in me throughout this journey. Additionally, I thank my mentor and close friend, Sondra Marshall, Ph.D., who has provided invaluable advice and encouragement throughout my career.

I am grateful for the unconditional love and support of my parents, Elena and Jeffry Alperin. Thank you especially to my father for providing integral technical support to this project.

Last, and foremost, I express my indebtedness and appreciation to my husband, Marc, whose sacrifices, patience, and devotion buoyed me throughout this process.

CHAPTER 1

INTRODUCTION

Each year depression torments approximately 15 million adults, roughly 7% of the U.S. population (Kessler, Chiu, Demler, & Walters, 2005). Treatment for depression typically begins with psychotherapy and medication. However, psychopharmacological intervention appears ineffective for one-third to half of those suffering from severe depression (Rush et al., 2006). Furthermore, medications can have intolerable side effects including metabolic syndrome and increased risk for suicide. A recent large scale trial (commonly called the STAR*D trial) investigating four levels of psychopharmacological treatment for severe depression found that 67% of participants responded to medication across the four levels, with remission rates between 20 and 30% depending on the medication prescribed (Rush et al., 2006). These figures suggest that approximately one-third of people treated with antidepressant medications may not respond favorably even after several alternative medications are attempted. Another problem associated with medication is poor treatment adherence, which further complicates estimates of individual response to medication.

For patients with pharmacological-resistant depressive conditions electroconvulsive therapy (ECT) is the most effective treatment (UK ECT Review

Group, 2003; Kho, van Vreeswijk, Simpson, & Zwinderman, 2003). Two multisite collaborations (Consortium for Research in ECT, 2001 and Columbia University Consortium, 2006) found remission rates between 55% (Sackeim et al., 2001) and 64% (Kellner et al., 2006) for ECT which compare favorably to the initial 30% remission rate with citalopram, as well as remission rates of 23% with bupropion, 21% with sertraline, and 25% with venlafaxine for patients in the STAR*D trial who did not initially respond to citalopram (Rush et al., 2006). These data strongly support the superior clinical efficacy of ECT over psychopharmacological approaches for treatment-resistant depression.

ECT involves the application of electrodes to the head. Through those electrodes, electrical charges are delivered to induce convulsion. Currently, ECT is administered to over 100,000 patients per year in the U.S. (Hermann, Dorwart, Hoover, & Brody, 1995), and an estimated 1 million patients per year outside the U. S. (Prudic, Olfson, & Sackeim, 2001). However, considering that medications are ineffective for at least 30% of people suffering from depression, about 3 million patients per year are left without some type of treatment, including those who might be potentially beneficial in reducing their symptoms.

Efficacy, Use, and Perception of ECT

Despite its clinical efficacy, ECT is underutilized. In a commentary on ECT published in the *Journal of the American Medical Association* in 2007, Fink and Taylor suggested several hypotheses accounting for the underuse of ECT in the U.S. One such factor contributing to ECT's underuse is that medical schools lack

preparation and education emphasizing ECT as a viable treatment option, as it is not a required subject of study in U.S. medical schools. Further, despite clear research support ECT is not a required competency domain in psychiatric residency training. Additionally, there is little formal regulation of ECT practice in the U.S.

Another barrier to ECT's widespread application is that U.S. approved devices have a limited energy range. In some cases, this limitation may prevent patients from being treated at the seizure thresholds required for effective treatment. This is a problem, especially for older patients, many of whom demonstrate higher seizure thresholds. Devices approved for use in Canada and Europe can deliver twice the energy of approved U.S. instruments, presumably improving treatment outcomes. Finally, Fink and Taylor (2007) point out that, despite well-documented efficacy and safety, ECT continues to be stigmatized and is primarily employed as a last-resort treatment option.

The poor image of ECT in both public and professional opinion revolves around the presumed effects of ECT on memory and other cognitive functions. Even though most research in this area suggests that any adverse effects are mild and short in duration, the opposite perception continues to be the primary barrier to broad application of ECT. In fact, the social stigma accompanying memory impairment and the fears associated with induced grand mal seizures likely lead many patients to decline ECT treatment each year. Unfortunately, this number has not been quantified in the research.

In an investigation of patient opinion about ECT, Malcolm (1989) interviewed 100 patients who were due to receive ECT. He found that approximately 60% feared the procedure. Specifically, patients were afraid of brain damage and memory loss. In posttreatment interviews, Malcolm also found that over 50% of the ECT patients reported side effects, with memory problems listed as their most common complaint.

A more recent investigation involving the review of 26 studies of patient perspectives on ECT found that over one third of patients reported significant memory loss after treatment, despite the lack of objective findings of memory impairment on standardized neuropsychological tests (Rose, Wykes, Leese, Bindman, & Fleischman, 2003). The authors of this study theorized that the contradiction between neuropsychological test findings and patient perspectives is a result of test choice. They point out that the neuropsychological measures commonly administered in ECT studies have typically examined anterograde amnesia or memory problems related to learning new material, while most patients complain of retrograde amnesia, or memory problems related to information they learned or knew prior to treatment. Rose et al. also suggest that this contradiction may be due to a lack of standardized neuropsychological measures designed to assess retrograde amnesia.

Recent advancements in the delivery of ECT treatment, including the introduction of brief and ultrabrief electrical pulse techniques, precise patient specific dosage titration, and variations in electrode placement all appear to help

diminish the negative cognitive effects of ECT without sacrificing treatment effectiveness (Sackeim et al., 2009). Yet fears of cognitive effects of ECT still exist. Therefore, to help clarify these issues for both patients and their physicians, it is necessary to continually assess approaches to ECT treatment and ascertain detailed information concerning cognitive side effects and treatment effectiveness.

Focus on Electrode Placement

Since ECT was introduced in the 1930s, bitemporal (also referred to as bilateral) ECT, in which the electrodes are applied to both temples, has been the primary treatment modality. In response to widespread early findings that bitemporal ECT resulted in short-term memory loss and confusion, unilateral ECT was introduced in an effort to reduce these symptoms. In unilateral placement one electrode is placed on the temple above the cerebral hemisphere that is nondominant for language (usually the right), and a second electrode is placed near the vertex on the same side. Early findings suggested that unilateral placement spared memory functions, but was less effective in alleviating depression than bitemporal placement (UK ECT Review Group, 2003), although more current findings suggest right unilateral ECT can have nearly equivalent efficacy if delivered at much higher intensity (Sackeim et al., 1993). A third electrode placement was introduced by Inglis (1969). In light of his review of bitemporal and unilateral ECT, Inglis proposed that a more anterior, bifrontal placement of the electrodes might prove to be as effective as bitemporal and

unilateral placements while further sparing cognitive functions. This proposal was based on the premise that bifrontal ECT would avoid stimulation over the temporal lobes, which are known to be particularly important in the mediation of memory and learning. In bifrontal ECT electrodes are applied to the forehead above the eyes.

While bifrontal ECT has recently gained in popularity, research of it has remained limited, especially regarding its cognitive effects. This is in part due to the introduction of brief and ultrabrief pulse techniques; that is, procedures that are touted to reduce the cognitive effects of bitemporal ECT and therefore restore bitemporal placement to its original stature as the preeminent choice in clinical practice. Yet, the issue of effectiveness and severity of cognitive side effects of bifrontal ECT has not undergone the type of scrutiny to which other ECT methods have been subjected. As a result, the current study proposed to not only investigate the effectiveness of bifrontal ECT, but conduct a rigorous examination of the cognitive effects of this type of ECT treatment. To ensure as natural an approach as possible, bifrontal ECT was examined within the context of a typical treatment course for severe depression in a university-based psychiatric hospital.

Before reviewing the current study, a brief review of the research on the effectiveness of ECT in treating depression and the cognitive effects associated with differing electrode placements is in order.

Overview of ECT Research

Effectiveness of ECT in Treating Depression

The UK ECT Review Group recently conducted a meta-analysis of the published work on the efficacy and safety of ECT, comparing ECT to simulated ECT or pharmacotherapy, and comparing different electrode placements in ECT treatment. They concluded that treatment with ECT was significantly more effective than pharmacotherapy and that bitemporal ECT was moderately more effective than unilateral ECT (UK ECT Review Group, 2003). Furthermore, high dose ECT was described as more effective than low-dose procedures. Based on the findings of Sackeim et al. (2001), this review also reported that relapse rates were high following initial response to ECT.

Similarly, a meta-analysis conducted by Kho et al. (2003) also found superiority for ECT over medication treatment and some evidence that psychosis predicted better response to ECT. A study conducted by Prudic, Olfson, Marcus, Fuller, and Sackeim (2004) found comorbid personality disorders were associated with poorer ECT response.

The American Psychiatric Association's (2010) *Guidelines for the Treatment of Depression* reported that the remission rates associated with ECT were between 70% and 90% in clinical trials. However, when investigated in community settings (general hospital ECT programs and outside of randomized controlled clinical trials), Prudic et al. (2004) found remission rates between 30% and 47% (with remission defined as a 60% or greater drop in HAM-D scores

from pre- to posttreatment and posttreatment scores less than 10). As stated above the two multisite studies reported remission rates ranging from 55 to 64% (Kellner et al., 2006; Sackeim et al., 2001). Prudic et al. also followed patients for 24 weeks after ECT treatment and found that among initial remitters the relapse rate was 64.3% (with relapse defined as an increase of at least 10 points in HAM-D scores from posttreatment to follow-up and minimum HAM-D scores of 16 for 2 consecutive weeks).

Grunhaus, Hirschman, Dolberg, Schreiber, and Dannon (2001) also investigated relapse by tracking patients for 3 months who had successfully responded to a course of right unilateral or bitemporal ECT (response defined as HAM-D scores ≤ 10 and/or post-ECT Global Assessment Function Scale scores ≥ 60 for 2 consecutive weeks). They found 10 of 35 patients relapsed within the 3-month follow-up period (relapse defined as a return of at least 5 DSM-IV symptoms of Major Depressive Disorder and HAM-D scores ≥ 16), yielding a relapse rate of 28.5%. Previously, Sackeim et al. (1993) reported a 58% relapse rate among the 70 patients in their study who were initially classified as being responders to a course of bitemporal or right unilateral ECT. More than three-quarters of these relapses occurred during the first 6 months following the completion of ECT. Sackeim et al. found no difference between electrode placements concerning relapse rates.

In summary, ECT is proven to be an effective treatment for severe depression, especially when individuals are at significant risk for suicide and

display psychotic symptoms (UK ECT review group, 2003). But relapse rates are high, with estimates ranging from nearly one-third to over two-thirds of those individuals who respond to the treatment.

Cognitive Effects of ECT

Despite prevailing lay opinion that ECT causes many cognitive side effects, research has not been quite as definitive. An overarching theme found in the literature is that ECT induces varying levels of anterograde and retrograde amnesia (Lisanby, 2007) and subjective memory complaints (Squire & Slater, 1983). Anterograde amnesia refers to difficulty remembering newly learned material, while retrograde amnesia refers to disturbances in memory for events or information learned prior to treatment.

Concerning nonmemory cognitive side effects, empirical findings have been varied. Some studies reported differences between ECT and non-ECT treated patients on mental status and other cognitive measures (Calev, Gaudino, Squires, Zervas, & Fink, 1995) while others failed to demonstrate any negative nonmemory cognitive effects (Schulze-Rauschenbach et al., 2005). To further complicate issues, findings are often not comparable, due to significant differences in the number of ECT sessions administered, variations in electrode placement, and significant variability in the neuropsychological instruments utilized to assess cognition. These factors make general conclusions concerning the cognitive effects of ECT difficult. Despite these challenges, numerous studies have been conducted in an attempt to clarify these issues. Below, the major

findings from bitemporal and unilateral studies of ECT are presented, followed by a review of the literature specifically focusing on bifrontal ECT.

Cognitive Effects of Bitemporal and Right Unilateral ECT

In a study comparing three groups of patients, those receiving bitemporal ECT, right unilateral ECT, or no ECT, Squire and Slater (1983) found patients' subjective reports of memory problems were higher for the bitemporal ECT group than for the control group immediately posttreatment. They found no differences between right unilateral placement and control groups. At 7 months follow-up, both ECT groups reported significantly higher subjective memory complaints than the control group. These findings suggested that patients treated with both bitemporal and right unilateral ECT perceive lasting problems with their memory. These findings are important, since ECT studies often fail to demonstrate impairments in memory on standardized cognitive measures, despite patients' subjective complaints of memory impairment following a course of ECT treatment.

In a comparison of right unilateral ECT (n = 14), transcranial magnetic stimulation (rTMS, n = 16), and controls (n=15) in the treatment of major depression, Shulze-Rauschenbach et al. (2005) found that patients treated with right unilateral ECT showed greater anterograde memory problems at posttreatment testing than either the rTMS or healthy control groups. Specifically, following the presentation of an interference list, those treated with right unilateral ECT remembered fewer words from a target list on the Rey

Auditory Verbal Learning Test (AVLT) than did non-ECT treated patients. These findings indicated evidence of anterograde amnesia with right unilateral ECT.

Regarding retrograde amnesia, Schulze-Rauschenbach et al. (2005) found that right unilateral ECT patients were also disadvantaged compared to the rTMS and control groups. Specifically, they remembered fewer pictures and made more errors recalling words from visual and verbal stimuli presented prior to treatment. However, no differences were found concerning autobiographical memory when assessed with the Autobiographical Memory Interview (AMI). These findings are consistent with findings that retrograde memory, although generally impaired following bitemporal ECT (McElhiney et al., 1997, Sackeim et al., 2007), is less impaired following right unilateral ECT. Consistent with the findings from Squire and Slater (1983) concerning subjective complaints, patients who received right unilateral ECT also subjectively reported more memory problems than the rTMS patients and controls (Schulze-Rauschenbach et al., 2005).

Shulze-Rauschenbach et al. found no differences between groups on any of the nonmemory cognitive measures administered in the study. Those measures included mental status, executive functions, auditory working memory, verbal fluency and processing speed as measured by the Mini-Mental State Exam (MMSE), Trail Making Test conditions A and B, Wechsler Digit Span subtest, Word Fluency test, and Letter-Number span tests, respectively. Their findings suggested that memory, but not other cognitive functions, appears susceptible to adverse treatment effects from right unilateral ECT procedures.

Furthermore, the rTMS group in the Shulze-Rauschenbach et al. study (2005) showed improvement for several memory measures from pre- to posttreatment. This suggests that when the rTMS patients' depression was alleviated, their memory may actually have improved, while the opposite effect was observed for the right unilateral ECT group, that is, their memory worsened below the initial levels associated with their depression.

These findings, that right unilateral ECT patients demonstrated no significant nonmemory effects, were inconsistent with previous conclusions drawn by Calev et al. (1995). These authors conducted a review of studies published since 1975 of only nonmemory cognitive effects of ECT and concluded that ECT did, in fact, cause nonmemory cognitive deficits for many patients. Despite recovery from depression, in which cognitive performance is expected to improve, Calev et al. found no improvement for ECT patients on several measures of cognition taken immediately posttreatment (48-72 hours). This was suggestive of nonmemory cognitive deficits resulting from ECT. Specifically, their review revealed that during the time immediately posttreatment, ECT patients deteriorated from baseline on measures of verbal fluency. Furthermore, they found a lack of evidence of improvement on measures of motor functions, perceptual and visuospatial functions, executive functions, and general intelligence testing from pre- to posttreatment for the ECT group. These findings suggested that many nonmemory functions may be impacted by ECT treatment in addition to the negative effects resulting from depression itself.

By the follow-up phases of these studies, which ranged from 1 week to 7 months posttreatment, Calev et al. (1995) found that nearly all measures improved over baseline or returned to baseline functioning. This suggested that the preponderance of negative effects of ECT on nonmemory cognitive processes found immediately posttreatment were alleviated within a brief period of time. The authors asserted that results concerning frontal lobe functioning (executive processes) were inconclusive and required further exploration. Further, the studies reviewed by Calev et al. employed either bilateral or right unilateral ECT electrode placement, but the authors made no distinctions between the two placements in terms of their differing cognitive effects. Therefore, from their review, it is not possible to make conclusions concerning nonmemory cognitive impairments due to different electrode placements. Nevertheless, the conclusion that any nonmemory cognitive impairments observed immediately posttreatment appear short in duration, regardless of electrode placement, is an important contribution of their review.

Sackeim et al. (2007) recently conducted a large-scale, prospective study of memory and other cognitive effects of ECT. In the study, 347 patients received either bitemporal or right unilateral ECT. The patients were evaluated pretreatment, immediately posttreatment, and approximately 6 months following treatment cessation. An extensive neuropsychological test battery was administered each time. The battery included measures of mental status (MMSE), psychomotor functioning (simple, choice, and Stroop reaction time

tasks), anterograde learning and memory (Complex Figure Test and the Buschke Selective Reminding Test), and retrograde amnesia (Autobiographical Memory Interview - Short Form).

A prominent finding of Sackeim et al. (2007) was that there were differences on measures of mental status, psychomotor speed, and retrograde amnesia between people receiving ECT at each treatment facility largely due to variations in ECT electrode placement and stimulation techniques. Specifically, the use of sine wave stimulation and bitemporal electrode placement were associated with greater short-term and long-term cognitive deficits. In particular, compared to brief pulse stimulation, sine wave stimulation had a greater negative effect on psychomotor response speed for two of the three reaction time tasks immediately posttreatment and at 6 months follow-up. In terms of memory effects, patients treated with bitemporal ECT had significantly greater amnesia for autobiographical information at both immediate and follow-up testing points compared to right unilateral ECT patients. This was consistent with previous findings that right unilateral ECT results in fewer cognitive side effects than bitemporal ECT (Sackeim et al. 1993). Compared to the right unilateral group, the bitemporal ECT group showed an average of 3.4 times more forgetting from pre- to posttreatment, and 2.8 times more amnesia at 6 months follow-up when assessed with the Autobiographical Memory Interview - Short Form (AMI). These findings suggest substantial deficits in retrograde memory for patients treated with bitemporal ECT.

In summary, the research suggests that memory dysfunction is the main cognitive impairment that may result from ECT treatment. Retrograde amnesia is the most common persistent adverse effect. Any nonmemory cognitive effects observed appear to be transient in nature. Furthermore, these studies show evidence that bitemporal ECT results in greater memory impairment than right unilateral ECT, which itself results in greater memory impairment than non-ECT treatments. Subjectively, patients often seem to report significant levels of memory impairment and confusion that research has failed to quantify.

Effectiveness and Cognitive Effects of Bifrontal ECT

Bifrontal electrode placement was initially adopted to avoid direct stimulation of the temporal and hippocampal areas, which are known to mediate human learning and memory. Unfortunately, research is not comprehensive concerning the effectiveness and cognitive effects of ECT conducted in this fashion. Some have suggested that the frontal lobe activation resulting from bifrontal electrode placement may have equally adverse consequences for executive functions as bitemporal placement has for memory functions (Crowley, Pickle, Dale, & Fattal, 2008). There is limited research into the effects of bifrontal ECT, specifically its effects on frontal lobe or executive functions. In fact, two recent meta-analytic reviews of the efficacy and safety of ECT failed to address bifrontal placement at all, reviewing only those studies employing bitemporal or right unilateral electrode placement (Kho et al., 2003; UK ECT Review Group, 2003). The limited number of studies investigating bifrontal electrode placement

in ECT are reviewed below.

In the Crowley et al. (2008) review of the research investigating the efficacy and cognitive side effects of bifrontal ECT the authors concluded that this electrode placement has clinical efficacy at least comparable to the traditional placements of right unilateral and bitemporal in treating severe depression. A recent study by Kellner et al. (2010) corroborated these findings by demonstrating that all three electrode placements are effective antidepressant treatments when administered at appropriate electrical dosing, although bitemporal placement resulted in more rapid symptom reduction. Similarly, Bailine et al. (2000) and Letemendia et al. (1993) concluded that bifrontal electrode placement was as efficacious in relieving depression as bitemporal and right unilateral placement, while resulting in less cognitive impairment. Based on studies conducted by Bailine et al. (2000) and Ranjkesh, Barekatain, and Akuchakian (2005) that found higher Mini-Mental State Exam (MMSE) scores for bifrontal versus other electrode placements, Crowley et al. concluded that bifrontal ECT produced fewer cognitive side effects than other electrode placements.

In an attempt to assess the clinical efficacy of bitemporal and bifrontal placements, Bakewell, Russo, Tanner, Avery, and Neumaier (2004) conducted an analysis of 76 patients' charts. The researchers concluded that, compared to bitemporal ECT, bifrontal ECT resulted in less impairment in cognitive variables such as confusion, disorientation, memory loss, and the need for assistance in

daily routines. An obvious limitation of the Bakewell et al. (2004) study, however, is its lack of standardized measures assessing cognitive impairment, despite the fact some might consider this method a strength, given the limitation of standardized measures in capturing the subjective experiences and adaptive behaviors of patients (behaviors that were investigated by Bakewell et al.).

To date, Lawson et al. (1990) and Kellner et al. (2010) have conducted the most in-depth studies designed to assess the cognitive effects of bifrontal ECT. Both studies investigated the differential effects on cognition of all three electrode placements in ECT.

Lawson et al. (1990) administered measures of verbal intelligence, verbal memory, nonverbal intelligence, and planning and sequencing to individuals in all three electrode placements groups. Verbal intelligence was evaluated by combining the Wechsler Adult Intelligence Scales - Revised (WAIS-R) subtests of Information and Vocabulary to create a composite score yielding a Verbal IQ. The researchers found that immediately following six treatments, the right unilateral and bifrontal groups performed superior to the bitemporal group on this measure of Verbal IQ, but by 7 days and 3 months posttreatment all differences between verbal functions for the three electrode placements had diminished. They also created a composite score for verbal anterograde memory by combining the Wechsler Memory Scale logical memory immediate and delayed recall conditions. Those results found that both the right unilateral and bifrontal groups performed superior to the bitemporal group on measures of anterograde verbal memory

immediately posttreatment, but not at 7 days or 3 months follow-up. The authors therefore concluded, despite observations of immediate differences in verbal functioning and anterograde memory, that no lasting cognitive differences were found between the three variations in electrode placements.

To the contrary, the more recent study conducted by Kellner et al. (2010) found that the bifrontal group scored inferior to the other two electrode placements in verbal anterograde memory (AVLT immediate and delayed tests), but that there were no differences between electrode placements in nonverbal anterograde memory. (The latter study used the Rey Auditory Verbal Learning Test (AVLT) to assess verbal anterograde memory and the Rey-Osterrieth and Taylor Complex Figure Tests to assess nonverbal anterograde memory.) Also contrary to earlier findings, Kellner et al. identified no advantages to right unilateral ECT in memory functions when compared to bitemporal placement. Regarding retrograde memory, Kellner et al. reported a trend toward inferiority of scores in the bifrontal group compared to right unilateral and bitemporal ECT groups on the Autbiographical Memory Interview. However, these results were not statistically significant.

Lawson et al. (1990) also examined nonverbal reasoning after ECT. The researchers found no differences between the three electrode placements in nonverbal intelligence as assessed by combining the WAIS-R Block Design and Object Assembly subtests into a composite score.

The Trail Making Test was used to evaluate the executive functions of

planning and sequencing after ECT in the studies of both Lawson et al. (1990) and Kellner et al. (2010). As with nonverbal functions, there were no reliable group differences found at any point between the three electrode placements. Kellner et al. also administered the Category Fluency test, Stroop Color Word Test, the Controlled Word Association Test, and the D-KEFS Sorting Test to assess executive functions. They found no evidence of differential effects for any of the three electrode placements.

Eschweiler et al. (2007) and Heikman et al. (2002), much like Kellner et al. (2010), found no results supporting the conclusion that bifrontal ECT results in less memory impairment compared to other electrode placements. In the study conducted by Eschweiler et al., 92 patients received six right unilateral ECT treatments or six bifrontal ECT treatments over a 3-week period. The findings suggested equal clinical efficacy in reducing depression for the two treatments, and no differences in mental status between them as measured with the MMSE. However, a shortcoming of their study relates to the relatively small number of treatments provided (6), as a typical ECT series ranges from 6 to 12 ECT treatments. Similar to Eschweiler et al., Heikman et al. found no differences in MMSE scores between three randomized groups who received high-dose right unilateral ECT, moderate-dose right unilateral, or low-dose bifrontal ECT.

In terms of clinical efficacy, Heikman et al. found more clinical improvement in depression symptoms, as rated by the HAM-D, for the high-dose right unilateral group compared to the moderate-dose right unilateral or low-dose

bifrontal groups. Results of these studies challenge findings that bifrontal ECT is associated with fewer cognitive side effects and comparable efficacy when compared to the other two groups. Yet these conclusions are limited by the assessment of cognitive functions only with the MMSE.

In summary, few studies have done a thorough job of investigating the cognitive effects of bifrontal ECT. What is clear is that bifrontal ECT is at least as efficacious as bitemporal and right unilateral ECT when administered at the proper dosing. The most recent investigation by Kellner et al. (2010), which compared the cognitive effects of all three placements, suggests that bifrontal ECT may actually result in greater anterograde amnesia for verbal information, but found no other statistically significant differences between electrode placements in other areas of cognition.

Purpose of Research

This study was designed to contribute to the limited scientific literature regarding the effectiveness and cognitive side effects of bifrontal ECT. Although bifrontal electrode placement has been gaining in popularity, there have been few investigations of the cognitive side effects of ECT conducted in a thorough fashion. Given concerns about side effects of ECT, in particular, potential persistent problems with memory, the following research questions were addressed in the current study.

Research Questions

1. How effective is bifrontal ECT in alleviating symptoms of depression immediately posttreatment and at 1-month follow-up?
2. Do participants treated with bifrontal ECT display difficulties with retrograde and anterograde amnesia immediately posttreatment and at 1-month follow-up?
3. What are the effects of bifrontal ECT on participants' performance on measures of executive functioning immediately posttreatment and at 1-month follow-up?
4. What are the effects of bifrontal ECT on participants' performance on measures of processing speed immediately posttreatment and at 1-month follow-up?

CHAPTER 2

METHOD

Participants

The present study was initially approved as part of a larger pilot study led by Howard Weeks, MD, a faculty member in the Department of Psychiatry at the University of Utah and psychiatrist at the University Neuropsychiatric Institute. Weeks' study set out to investigate the effectiveness and cognitive side effects of both bifrontal ECT and an experimental treatment for depression involving repeated Isoflurane anesthesias. The Institutional Review Board at the University of Utah was confirmed on 1/23/2008, (IRB #00025750). A substudy of the larger study aiming to investigate only the effectiveness and cognitive side effects of bifrontal ECT received Institutional Review Board approval on 4/21/2010 (IRB #00025750). The data used for the present study were drawn from both the larger study and substudy. Sources and selection criteria for participants of the present study are discussed below.

Recruitment and Selection

Participants were recruited from among patients referred for ECT through a university-based psychiatric hospital ECT program, where approximately 2,000

treatment sessions are administered each year. Individuals from 18 to 65 years of age who displayed significant unipolar or bipolar depression and had been recommended by a psychiatrist for ECT treatment were invited to participate. Nineteen participants who had agreed to receive ECT treatment consented to participate in the current study. After consent was provided, 1 participant withdrew from the study while attempting to complete baseline neuropsychological testing due to extreme emotional distress, and a 2nd participant withdrew just prior to follow-up testing, reporting disappointment with the effects of the ECT treatment. This individual indicated he did not wish to have his baseline or posttreatment data included for analysis. Of the 17 remaining participants, 11 were male and 8 female. The study participants ranged in age from 23 to 62. Nine were involved in inpatient treatment, and 10 received treatment in an outpatient setting. All participants, however, had a documented history of severe depression unsuccessfully treated by at least two different medications during a 2-year period or more and had severe enough depression at the time of this study to warrant psychiatrist referral for ECT. Further, patients being treated in outpatient care were offered the choice to enroll in a series of Isoflurane anesthesia or bifrontal ECT treatments, while patients receiving inpatient care were offered participation in the bifrontal ECT condition only. It should be noted that all participants in the current study were maintained on usual medical treatment, including psychopharmacotherapy and psychoptherapy, while undergoing ECT.

Exclusionary criteria used in the study included 1) a diagnosis of primary psychotic disorder, dysthymia, or personality disorder; 2) significant premorbid cognitive impairment; 3) unstable symptomatic coronary artery disease, poorly compensated congestive heart failure, history of transient ischemic or neurologic signs during the past year, or history of susceptibility to malignant hyperthermia; 4) any other contraindication to Isoflurane anesthesia; or 5) deemed incompetent to provide consent.

Setting and Procedures

Assessment of study participants took place in the ECT wing or on the inpatient ward of a university-based psychiatric hospital. Testing was conducted in a one-to-one format. Data were collected over a period of 15 months from 2009-2010.

Each potential participant was given a full verbal explanation of the study procedures including risks, benefits, and alternatives, and offered a copy of their signed written consent form (Appendix A). Potential participants were given the opportunity to review the consent form and discuss any questions or concerns with their own psychiatrist, study investigators, or others if necessary, a minimum of 1 day prior to beginning the study treatment procedures. Anyone judged by the referring psychiatrist or study psychiatrist as incompetent to give informed consent for the study was considered ineligible for participation (incompetence as defined by the inability to understand the risks associated with the procedures or alternative treatments, such as impaired cognitive functioning

or severe psychosis).

Participants received a series of ECT treatments, ranging from 7 to 12 per participant, over a 2 1/2- to 3 1/2-week period. All treatments were administered at a university-based psychiatric hospital. Participants received standard recommended monitoring and follow-up health care from hospital physicians and medical staff.

Participants completed a battery of psychiatric and neuropsychological measures (described below) within the week prior to beginning treatment and within 24 to 48 hours after treatment concluded. Follow-up testing was also conducted approximately 1 month (4 to 5 weeks) after the end of the treatment. Of the 17 participants, 13 completed all test measures. One participant could not complete one computerized test that relied on speeded verbal fluency of the English alphabet because English was not his first language and he demonstrated poor alphabetic fluency. Two participants' computerized data could not be used due to technical failure of the computerized testing equipment. One participant who resided over 5 hours away could not return to the university-based hospital for follow-up testing. Therefore computerized data and pencil paper tests (Coding and Symbol Search from the Wechsler Adult Intelligence Scale – III) could not be administered. Examiner error resulted in invalid test administration of the Logical Memory I and II subtests from the Wechsler Memory Scale – Third Edition at posttreatment for the 4th participant. Therefore, a limited number of data points were missing from the neuropsychological test

data.

Participants were assigned an identification number to which all data were linked. Except for birth date, which was required for scoring many of the measures, all personal identifiers were removed from the data used in the analyses. The data were kept in a secure location in the office of the principal investigator of the larger study, a psychiatrist at the hospital where the study took place.

The primary investigator and two research assistants trained in neuropsychological assessment administered all measures according to standardized procedures. Participants were observed for signs of fatigue or distress during the assessments and offered opportunities for breaks. All protocols were scored by the individual administering the testing and the primary investigator entered the data into a secure database (linked only to participant identification number).

Measures

Participants in the study underwent psychiatric and neuropsychological assessments, listed in Table 1. Specifically, participants completed a series of standardized cognitive tests designed to assess memory, mental processing speed, executive functioning and motor control, lasting approximately 50 to 60 minutes. At pretreatment only, participants also completed the Wechsler Test of Adult Reading (WTAR), a 3-minute, 50-item oral reading task that provides an estimate of premorbid cognitive status. At pretreatment, posttreatment, and

Table 1

Performance Measures

Domain	Measures
Depression	Hamilton Depression Inventory – 24 Item (HAM-D)
Mental Status	Mini-Mental State Exam (MMSE)
Retrograde Amnesia	Autobiographical Memory Interview – Short Form (AMI)
Anterograde Amnesia	Hopkins Verbal Learning Test – Revised (HVLT-R, Immediate Recall and Delayed Recall)
	Wechsler Memory Scale – III, Logical Memory I & II (WMS-III, LMI & LMII)
Processing Speed	Wechsler Adult Intelligence Scale – III (WAIS-III) Digit-Symbol Coding and Symbol Search Subtests
Executive Functioning and Motor Control	Delis-Kaplan Executive Functioning Scales (D-KEFS), Verbal Fluency Test (FAS)
	Behavioral Dyscontrol Scale - Electronic Version (BDS-EV), Alphanumeric Sequencing Test, Simple Choice Reaction Time Test, Branching Go No Go Test
Premorbid Cognitive Level	Wechsler Test of Adult Reading (WTAR)

follow-up, participants completed 12 tests that comprised the study's testing battery, including the Hamilton Depression Inventory, Mini-Mental State Exam, Autobiographical Memory Interview, Hopkins Verbal Learning Test - Revised, Wechsler Memory Scale - Third Edition Logical Memory subtests, Wechsler Adult Intelligence Scale - Third Edition Processing Speed subtests (Symbol Search and Digit Symbol Coding), four subtests from the Behavioral Dyscontrol Scale - Electronic Version, and the FAS test of verbal fluency. Participants also responded to two questions designed for the study assessing subjective memory impairment and perceived treatment effectiveness (Appendix B). The subjective memory impairment question was administered at all three testing sessions, while the treatment effectiveness question was only administered at follow-up testing.

Depression

The Hamilton Depression Inventory (HAM-D; Hamilton, 1967) was used to assess depressive symptomatology in all participants at pretreatment, posttreatment, and follow-up testing sessions. This study utilized the 24-item interview which rates the severity of symptoms observed in depression such as low mood, insomnia, agitation, anxiety and weight loss. The questionnaire is one of the most commonly used scales for rating depression in medical research. The investigator rates the patient by interviewing them and observing the patient's symptoms. Each question has from three to five possible responses that increase in severity. The total score represents a sum of the values for the questions. Scores under nine indicate the absence of diagnostically significant depression.

Scores ranging from 10 to 19 indicate mild depression symptomatology, 20 to 29 indicate moderate depression, and scores above 30 are interpreted as indicating severe depression. The maximum score one can receive on this measure is 66.

Mental Status

The Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) was given to assess mental status. This is a brief 30-point questionnaire that is used to screen for cognitive impairment in many clinical settings. The MMSE includes simple questions and items assessing several areas, including time and place orientation, immediate auditory memory, motor functioning, and visual perception. Any score greater than or equal to 25 points (out of 30) is considered normal (intact), and scores below 25 points may indicate severe (≤16), moderate (17-21), or mild (21-24) cognitive impairment.

Retrograde Memory

Retrograde amnesia was assessed with the Autobiographical Memory Interview - Short Form (AMI, McElhiney, Moody, & Sackeim, 1997). This instrument was developed specifically for the purpose of examining the nature of amnesia following ECT, and allows the quantification of retrograde amnesia following ECT treatment. To accomplish this, the participant was asked a series of detailed autobiographical questions prior to ECT. The questions probed for specific details for six sets of events or experiences, most of which occurred during the previous year. The six domains inquired in detail about the

participant's most recent employment, birthday celebration, New Year's Eve activities, information about a close relative, recent travel, and most recent physical complaint for which they sought medical care. Each of these six domains contained six specific questions (i.e., Where did you celebrate your last birthday?) These same questions were asked again at posttreatment and follow-up. Thus, the participant's answers prior to treatment were used as a template against which subsequent answers were compared. The comparison of the posttreatment answers with the answers given prior to treatment yielded "amnesia scores" in the form of percentiles. Individual norms have not been developed for this instrument, yet it remains the primary outcome measure for personally relevant autobiographical memory currently utilized in ECT research.

Anterograde Memory

Two separate tests were administered to measure verbal learning and memory. These include the Hopkins Verbal Learning Test – Revised Immediate Recall and Delayed Recall conditions (HVLT-R; Brandt & Benedict, 2001) and the Wechsler Memory Scale - Third Edition Logical Memory subtests, Immediate and Delayed (WMS-III LM I & II; Wechsler, 1997). The HVLT-R is a word list-learning task where 12 words are presented over three learning trials. At the end of each trial the participant provided as many of the words from the list as he/she could recall. After a 20- to 25-minute time delay, the participant was asked to recall as many words as they were able from memory. The final task required participants to discriminate which words were on the original list from a longer list in a forced

choice (yes versus no) paradigm. Raw scores were converted to *T*-scores (*M*=50, *SD*=10) to yield scores for total recall (a composite score from the first three trials), delayed recall, % retention, and recognition discrimination. Benedict, Schretlen, Groniger, and Brandt (1998) conducted test-retest reliability analyses in older adults, with a mean test-retest interval of 6 weeks. Reliability for the four primary HVLT-R variables were .74 for total recall, .66 for delayed recall, .39 for % retention, and .40 for recognition discrimination.

The WMS-III Logical Memory subtests were used to assess auditory recall under immediate and delayed conditions. In the immediate condition (Logical Memory I) the participant listened to two stories and retold the details of the stories over three trials, one trial for story 1 and two trials for story 2. The participants' raw score for all three trials was summed and converted to a subtest scaled score (*M* = 10, *SD* = 3). After a 25- to 35-minute delay (Logical Memory II), the participant was asked to retell the details of the two stories. In this case, the raw scores from the two trials were summed and converted to scaled scores. The split-half reliability coefficients, providing measures of internal consistency, were reported in the manual for both subtests (Wechsler, 1997b). Averaged across all age groups, the reliability coefficient for Logical Memory I was .88 and for Logical Memory II was .79, indicating high internal consistency. Test-retest reliability coefficients, providing estimates of the subtest stability over time, were also reported. Averaged across all age groups, the test-retest reliabilities for Logical Memory I and Logical Memory II were .77 and .76, indicating moderately

high stability over time.

Shapiro, Benedict, Schretlen, and Brandt (1999) examined the correlations between HVLT-R total recall, delayed recall, and percent retention, and comparable measures from the Logical Memory subtests of the Wechsler Memory Scale - Revised (WMS-R). They found the highest correlation with HVLT-R total recall with Logical Memory I (r=.75) and the highest correlation with HVLT-R delayed recall with Logical Memory II (r=.77). This suggests that the HVLT-R total recall and WMS-R Logical Memory I subtest may be capturing similar facets of immediate anterograde memory, while the HVLT-R delayed recall and WMS-R Logical Memory II subtests may overlap in their measurements of delayed anterograde memory.

Processing Speed

Processing speed was assessed using the Digit Symbol-Coding (Coding) and Symbol Search subtests from the Wechsler Adult Intelligence Scale – 3rd Edition (WAIS-III; Wechsler, 1997a). Raw scores were converted to scaled scores (M=10, SD=3), and the two subtest scaled scores were combined to form a composite reflecting processing speed. This composite (Processing Speed Index) results in a standard score (M=100, SD=15) describing a person's speed of visual scanning, visual discrimination, and graphomotor speed. Both subtests are administered under a 2-minute time limit.

Reliability coefficients reported in the manual, in the form of test-retest reliabilities averaged across all age groups, were .86 and .79 for Digit Symbol-

Coding and Symbol Search, respectively. The Processing Speed Index demonstrated high test-retest reliability across all age groups with a coefficient equal to .89.

Executive Functioning and Motor Control

Four subtests from the Behavioral Dyscontrol Scale - Electronic Version (BDS-EV; Suchy, Derbidge, & Cope, 2005) were administered to assess various aspects of executive functioning and motor control. The BDS-EV comprises a series of subtests administered via computer. Participants responded to the tasks on a response box designed for use with this test battery. The subtests administered included Branching Go-No-Go, Push-turn-taptap, Alphanumeric sequencing, and Simple choice reaction time. Branching Go-No-Go, a test requiring subjects to respond differentially to shapes and squares, measured both reaction time and decision speed. Push-turn-taptap, a test requiring participants to rapidly perform a series of one or more hand movements from memory, provided a measure of motor programming, inhibition, and working memory. The Alphanumeric sequencing subtest, designed to measure aspects of working memory and visual scanning, required participants to complete a letter/number sequence by pushing buttons on both the left and right hand sides of the response box. The last test from the BDS-EV battery is the Simple choice reaction time task, measuring reaction time. In this task participants pushed a button as quickly as possible to match the color of a circle shown on the screen.

The tests of the BDS-EV have demonstrated adequate reliability on

measures of internal consistency, with Cronbach's alpha values ranging approximately from .70 to 87. Furthermore, Suchy, Derbidge, and Cope (2005) found moderate to strong convergent evidence with the Behavioral Dyscontrol Scale, a paper-pencil format from which the electronic battery was derived.

Verbal Fluency

The FAS verbal fluency test was administered and scored according to standard procedures set forth in the Delis-Kaplan Executive Functioning Scales (D-KEFS; Delis, Kaplan, & Kramer, 2001a). This test required participants to name as many words as they could beginning with the letters "F", "A", and "S" under 1-minute time constraints. The raw scores for each letter condition were summed and converted to standard scores using the D-KEFS norms (M = 10, SD = 3). According to the D-KEFS technical manual (Delis, Kaplan, & Kramer, 2001b), the letter fluency condition (FAS) has demonstrated strong split-half internal consistency measures with an average correlation of .85 for all the adult age groups. Similarly, the test has been shown to have adequate test-retest reliability for all ages (r=.80).

Premorbid Cognitive Level

Pretreatment cognitive functioning was estimated using the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001). This instrument, which was co-normed with the WAIS-III (and WMS-III), was designed to provide a measure of premorbid cognitive functioning prior to the onset of an injury or illness. Word

reading has been found to be relatively resistant to the negative impact of neurologic insult, including traumatic brain injury, and other illnesses or conditions that have been shown to affect cognitive ability, including depression.

The WTAR requires that a person read 50 words aloud. Raw scores are then converted to standard scores (M=100, SD=15) to estimate intellectual functioning. According to the WTAR manual, internal consistency measures using alpha coefficients range from .90-.97 for the different age groups in the U.S. standardization sample. Test-retest reliability coefficients have been shown to be similarly high, that is, .90 to .94. The reported correlation of the WTAR score with the WAIS-III Full Scale IQ score is .73 for the total standardization sample.

Subjective Questions

Two subjective questions were created for use in this study. The first asked participants to rate their memory over the past 24 hours on a scale of one to seven, with a one rating reflecting no observed memory difficulties and a seven rating reflecting severe observed memory difficulties. This question was administered at pretreatment, posttreatment, and follow-up testing sessions. The second question, administered only at follow-up, asked participants to rate the effectiveness of their treatment on a scale of one to seven, with one reflecting an opinion that the treatment was completely ineffective and seven completely effective.

Design

The larger ECT and Isoflurane study and neurocognitive effects substudy from which the data for this study were drawn represents a repeated measures design. The repeated measures factor involves the analysis of depression and cognitive effects of participants who received ECT over three points in the course of treatment: pretreatment, posttreatment, and follow-up.

Data Analyses

The performance of participants on individual measures was described using measures of central tendency and variability. Means and standard deviations of the continuous variables were calculated for the sample. Frequency of categorical variables (e.g., gender) was determined and tabulated for the sample. Range of scores was calculated for each measure. Research questions were addressed through repeated measures analysis of variance comparing mean differences across the three points in treatment with a statistical significance level of $p<.05$.

CHAPTER 3

RESULTS

Demographic Data

As seen in Table 2, the 17 participants who completed all phases of the study ranged in age from 23 to 62. Mean age of the 17 participants in the total sample was 41.71 with a standard deviation of 11.66. Data from 10 males (59% of the sample) and 7 females (41% of the sample) were included. Seven of these participants received treatments as part of their inpatient hospital care (41% of the sample) and 10 received outpatient treatment (59% of the sample). Premorbid cognitive level was assessed with the Wechsler Test of Adult Reading (WTAR). The mean WTAR score was 107.71, with a standard deviation of 8.99 and range from 87 to 125. WTAR scores falling between 85 and 115 are classified as average. Participants received between 7 and 12 treatments in their series, with an average of 9.06 treatments (*SD*=1.35). The majority of the participants in this study met the DSM-IV criteria for Major Depressive Disorder, severe and recurrent, without psychotic features, as their primary diagnosis. One individual received a primary diagnosis of Major Depressive Disorder, severe and recurrent, with psychotic features, and 1 received a primary diagnosis of Bipolar Disorder I. Secondary diagnoses included Generalized Anxiety Disorder

Table 2

Participant Demographics for Gender, Age, Premorbid Cognitive Level, Inpatient/Outpatient Status, and Number of Treatments Received

Demographic	Total Sample
Males (% of sample)	10 (59%)
Females (% of sample)	7 (41%)
Age – *M(SD)*	41.71 (11.66)
Premorbid Cognitive Level on WTAR– *M(SD)*	107.71 (8.99)
Inpatient Status (% of sample)	7 (41%)
Outpatient Status (% of sample)	10 (59%)
Number of Treatments – *M(SD)*	9.06 (1.35)

(4 individuals), Alcohol Abuse or Dependence (3), Cannabis Abuse or Dependence (3), Opoid Dependence (1), Obsessive Compulsive Disorder (1), Dysthymic Disorder (1), Anxiety Disorder NOS (3), Post-Traumatic Stress Disorder (2), and Panic Disorder without Agorophobia (1). Individual participant demographic data are displayed in Table 3.

Research Question 1

How effective is bifrontal ECT in alleviating symptoms of depression immediately posttreatment and at 1-month follow-up? Data from the HAM-D interview, displayed in Table 4, show that 15 of the 17 participants who completed the HAM-D prior to treatment had scores falling in the severely depressed range. According to Hamilton (1967), scores > 30 constitute severe depression, whereas scores of 20-29 indicate moderate depression, scores of 10-19 indicate mild symptoms, and scores $\leq$9 indicate no depression. Immediately posttreatment 8 participants had HAM-D scores in the range indicating no depression (score $\leq$ 9), 7 had scores in the mildly depressed range (scores 10-19), 1 demonstrated moderate depression (20-29), and 1 had severe depression $\geq$ 30. These data indicate that the majority of the participants responded to bifrontal ECT treatment. At 1-month follow-up, three HAM-D scores fell in the range indicating no depressive symptoms, seven in the mild range, six in the moderate range, and one in the severely depressed range.

Table 3

Individual Participant Demographic Data

Part. No.	Age / Gender	No. ECT Treatments	Treatment Setting	Primary Diagnosis	Secondary Diagnosis	Pre-ECT WTAR Score
1	60/Female	8	Inpatient	296.33: Major Depressive Disorder, Recurrent, Severe Without Psychotic Features	None	107
2	47/Female	8	Inpatient	296.33	Anxiety Disorder NOS, Panic Disorder Without Agorophobia	117
3	28/Male	10	Outpatient	296.33	Generalized Anxiety Disorder	105
4	32/Male	8	Outpatient	296.33	Generalized Anxiety Disorder, Alcohol Abuse	98
5	40/Male	8	Inpatient	296.33	Anxiety Disorder NOS	108
6	23/Male	10	Outpatient	296.33	Generalized Anxiety Disorder	87
7	62/Male	8	Inpatient	296.33	Alcohol Dependence, Cannabis Dependence	107
8	31/Female	9	Outpatient	296.53: Bipolar I Disorder, Most Recent Episode Depressed, Severe Without Psychotic Features	Opiod Dependence	106
9	31/Male	8	Inpatient	296.34: Major Depressive Disorder, Recurrent, Severe With Psychotic Features	Obsessive-Compulsive Disorder	109
10	43/Male	8	Outpatient	296.33	None	113
11	48/Male	9	Outpatient	296.33	None	119
12	47/Female	11	Outpatient	296.33	Dysthymic Disorder, Anxiety Disorder NOS	125
13	52/Male	12	Inpatient	296.33	Cannabis Dependence, Post Traumatic Stress Disorder	102
14	31/Female	10	Outpatient	296.33	Generalized Anxiety Disorder, Panic Disorder Without Agorophobia, Alcohol Abuse, Cannabis Abuse	117
15	45/Female	10	Outpatient	296.33	None	98
16	55/Female	7	Inpatient	296.33	Anxiety Disorder NOS, Post Traumatic Stress Disorder	107
17	34/Male	10	Outpatient	296.33	Anxiety Disorder NOS	106

Table 4

Classifications, Means, and Standard Deviations at Pretreatment, Posttreatment, and Follow-up for Hamilton Depression Inventory (HAM-D)

Classification	Pretreatment	Posttreatment	Follow-up
Number of HAM-D scores in "No Depression" Range	0	8	3
Number of HAM-D scores in "Mild Depression" Range	1	7	7
Number of HAM-D scores in "Moderate Depression" Range	1	1	6
Number of HAM-D scores in "Severe Depression" Range	15	1	1
Mean HAM-D Score (Standard Deviation)	37.18 (8.76)	10.12 (9.60)	15.12 (9.45)
Average % Reduction in Mean HAM-D Symptoms from Pretreatment		72.78%	59.33%

These data show that 10 participants, over half, demonstrated negligible or low levels of depressive symptomatology at the time of follow-up, whereas 7 participants demonstrated moderate to severe levels of depressive symptoms at follow-up, or one month following the cessation of ECT treatment.

According to some ECT researchers, response to treatment is defined as a 50% reduction in depressive symptoms on the HAM-D (Eschweiler et al., 2007; Kellner et al., 2010; Sackeim et al., 2007; Schulze-Rauschenbach et al., 2005). Results of the current study showed that 15 of the 17 participants (88.24% of the sample) who completed HAM-D interviews at all three assessment points had at least a 50% reduction in depressive symptoms as measured by the HAM-D interview posttreatment. At 1-month follow-up, 11 of the 15 participants initially considered responsive to treatment continued to demonstrate a 50% or greater reduction in symptoms, that is, 65% of the total sample were classified as responsive 1 month posttreatment. The 4 participants who were initially considered responsive to treatment but no longer responsive at 1 month follow-up all had scores within the moderate depression range. Two of the 15 individuals initially responsive to treatment could be considered to be relapsing, defined by Prudic et al. (2004) as an increase in HAM-D scores of at least 10 points from posttreatment to follow-up and a total HAM-D score greater than 16. According to this definition, 13% of the participants in the current study would be considered to have relapsed. Further, the current findings showed that 11.8% of those receiving bifrontal ECT, or 2 participants, were completely

nonresponsive to treatment.

In terms of participant mean scores across treatment, average HAM-D scores prior to treatment fell within the severe depression range (*M*=37.18, *SD*=8.76). At posttreatment, an average reduction in HAM-D scores of over 70% was observed (*M*=10.12, *SD*=9.60) with the mean score falling in the mild depression range. At 1 month follow-up average HAM-D scores increased slightly but still reflected over a 50% reduction in scores from the pretreatment baseline HAM-D measures (*M*=15.12, *SD*=9.45) with the mean continuing to fall in the mild depression range.

Data analyzed using a repeated measures ANOVA compared mean participant HAM-D scores from pretreatment, posttreatment, and follow-up testing and results are illustrated in Figure 1. Mauchly's test showed that the assumption of sphericity had been violated (ω=.558, p <.05); therefore, the degrees of freedom were corrected using the Greenhouse-Geisser correction. Results of this test revealed that the level of participant depression differed significantly at the three interview administrations, $F(1.39,22.20) = 58.209$, $p <$ .05, $\eta_p^2 = 0.784$. Post-hoc comparisons using the Bonferroni adjustment for significance indicated that the average HAM-D scores were significantly lower at posttreatment (10.12 ± 9.60) and follow-up (15.12 ± 9.453) compared to pretreatment (37.18 ± 8.76) with statistical significance for both comparisons (p < .05). Based on these data, bifrontal ECT resulted in a statistically significant

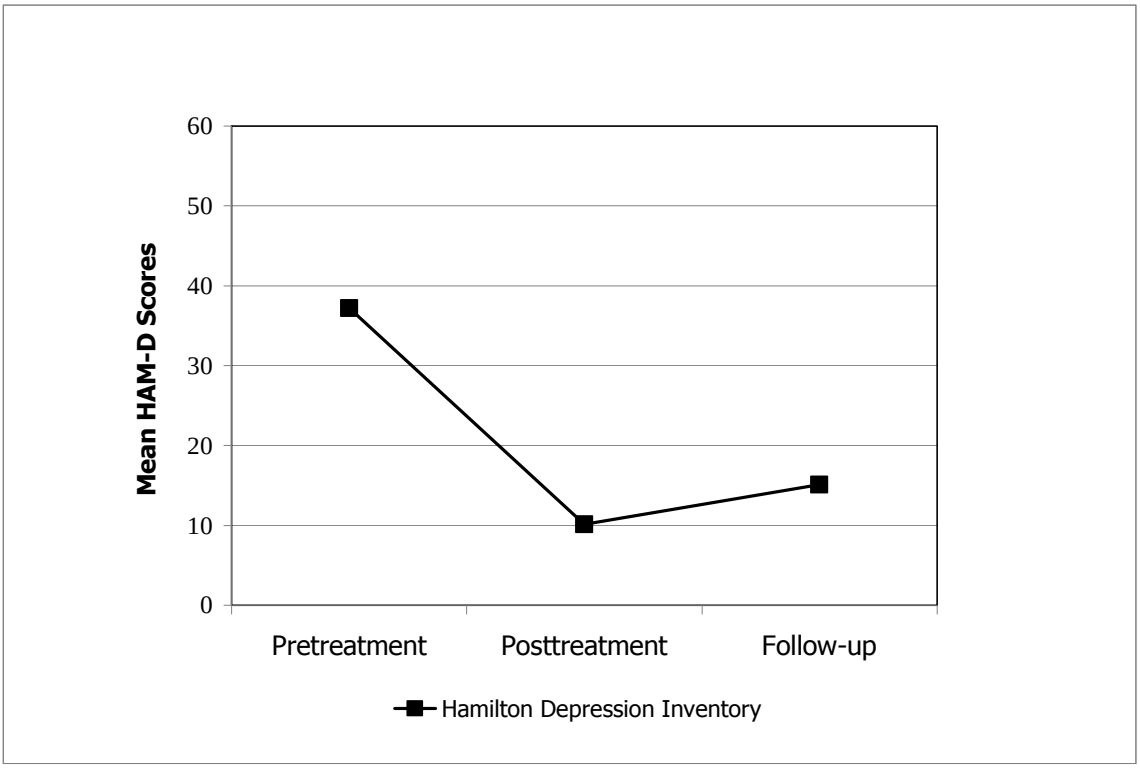

Figure 1. Group Comparison of Mean Scores on the HAM-D

* HAM-D values are classified as follows: 0-9 insignificant levels of depression, 10-19 mild depression, 20-29 moderate depression, >30 severe depression

reduction in participant report of depression from pretreatment to posttreatment (immediately following treatment and 1 month later). Post-hoc comparisons, on the other hand, showed an increase in participant report of depression on the HAM-D from posttreatment (10.12 ± 9.60) to follow-up (15.12 ± 9.45), findings that were statistically significant at the $p < .05$ level. These results show that, on average, participants' depressive symptoms increased from posttreatment levels by follow-up, that is, 1 month later; however, the mean level of depression at the time of follow-up was still significantly lower than the mean level prior to treatment. Two of the 15 participants (or 13.4%) who were initially considered to be responsive to treatment, however, were considered to have relapsed 1 month following the cessation of treatment, that is, had a 10-point or more increase in HAM-D scores, and a score at or above a 16 from posttreatment to follow-up.

Research Question 2

Do participants treated with bifrontal ECT display difficulties with retrograde and anterograde amnesia immediately posttreatment and at 1-month follow-up? This research question examined whether participants receiving bifrontal ECT treatment had retrograde amnesia, that is, had difficulty remembering information they knew prior to treatment, or anterograde amnesia; that is, difficulty remembering newly learned information. Data from the Autobiographical Memory Interview – Short Form, WMS-III Logical Memory I and II, and Hopkins Verbal Learning Test were used to analyze this question.

Comparisons of participant performance on the measures of both retrograde and anterograde memory can be found in Figure 2.

The Autobiographical Memory Interview – Short Form (AMI) represents the main measures of retrograde amnesia in the present study. Table 5 shows the means and standards deviations for the AMI.

A repeated measures ANOVA compared mean AMI scores from pretreatment, posttreatment, and follow-up to determine if there were any changes in autobiographical memory recall between the three performances. Results of the ANOVA demonstrated that AMI scores differed significantly across the three test administrations, $F(2,32) = 32.87$, $p < .05$, $\eta_p^2 = 0.673$. Post-hoc comparisons analyses using the Bonferroni adjustment for significance indicated that the average AMI scores were significantly lower at posttreatment (72.43 ± 17.93) and follow-up (68.74 ± 20.88) when compared to pretreatment AMI scores (100 ± 0.00), yielding statistically significant results for both comparisons ($p < .05$). Findings of significant retrograde amnesia immediately following ECT treatment and 1 month later are not unexpected, even with bifrontal electrode placement. This is a common finding in ECT studies, that is, ECT treatment can negatively impact a person's ability to remember past events long after the cessation of treatment (Kellner et al., 2010; McElhiney et al., 1997; Sackeim et al., 2007). In terms of anterograde amnesia, or the ability to recall newly learned information, several measures were used for assessment. The WMS-III Logical Memory Test, a verbal story memory task, has both an immediate (LMI) and

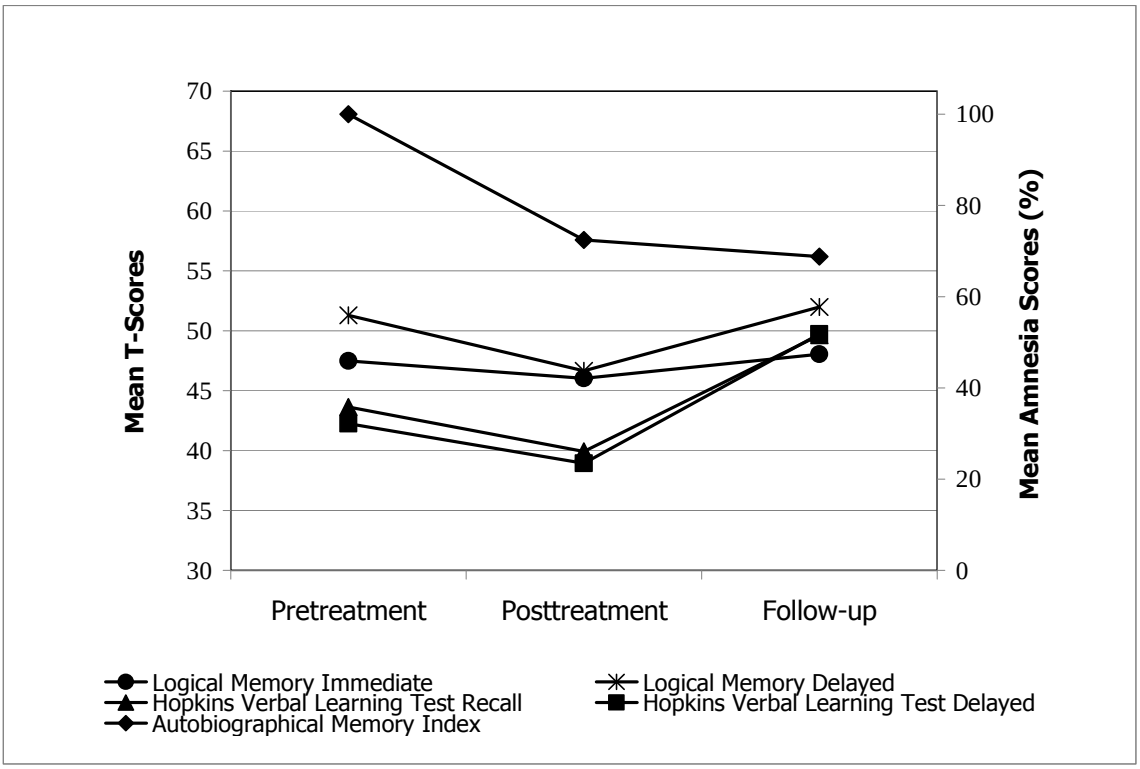

Figure 2. Group Comparison of Mean Scores on Measures of Anterograde and Retrograde Amnesia

* AMI scores are graphed on the secondary Y-axis; LMI & II scores were converted from scaled scores to *T*-scores for the purpose of this graph, average *T*-scores range from 40-60 (standard deviation = 10)

Table 5

Means and Standard Deviations at Pretreatment, Posttreatment, and Follow-up for the Autobiographical Memory Interview – Short Form (AMI-SF)

	Pretreatment	Posttreatment	Follow-up
Mean Autobiographical Memory Interview percentage Score (Standard Deviation)	100 (0)	72.43 (17.93)	68.74 (20.88)

delayed condition (LMII, given after a 25-minute time delay). Table 6 shows the means and standard deviations from the two Logical Memory tests.

A repeated measures ANOVA which compared mean scores for the immediate Logical Memory Test across treatment did not demonstrate a main effect for bifrontal ECT. In other words, there were no statistically significant changes in participants' immediate recall of a story between pretreatment, posttreatment, and follow-up testing.

Similarly, a repeated measures ANOVA for the delayed Logical Memory Test did not show a main effect for the treatment, suggesting that on average there were no significant changes in participants' delayed story memory between pretreatment, posttreatment, and follow-up testing.

The Hopkins Verbal Learning Test – Revised (HVLT), an auditory word list-learning task, has both an immediate (HVLT Recall) and a delayed condition (HVLT Delayed, given after a 20-minute time delay). The means and standard deviations of the HVLT-R immediate and delayed memory conditions can be found in Table 7.

A repeated measures ANOVA compared the mean scores between pretreatment, posttreatment, and follow-up testing for the HVLT Recall test and results are depicted above in Figure 2. The analysis revealed that participant average HVLT Recall test scores differed significantly between testing time points, $F(2,32) = 10.63$, $p < .05$, $\eta_p^2 = 0.399$. Post-hoc comparisons analyses using the Bonferroni adjustment for significance showed that the average HVLT

Table 6

Means and Standard Deviations at Pretreatment, Posttreatment, and Follow-up for the WMS-III Logical Memory I and II (LMI & LMII) Tests

	Pretreatment	Posttreatment	Follow-up
Mean Logical Memory I Score (Standard Deviation)	9.25 (2.57)	8.81 (3.60)	10.69 (3.01)
Mean Logical Memory II Score (Standard Deviation)	10.40 (2.67)	9.00 (4.99)	10.60 (2.13)

Table 7

Means and Standard Deviations at Pretreatment, Posttreatment, and Follow-up for the Hopkins Verbal Learning Test-Revised (HVLT-R)

	Pretreatment	Posttreatment	Follow-up
Mean HVLT-R Immediate Recall Score (Standard Deviation)	43.65 (13.37)	39.94 (14.16)	49.65 (11.77)
Mean HVLT-R Delayed Recall Score (Standard Deviation)	42.25 (13.74)	38.94 (14.00)	49.75 (10.22)

Recall scores were significantly higher at follow-up (49.65 ± 11.78) compared to both mean pretreatment scores (43.65 ± 13.37) and mean posttreatment scores (39.94 ± 14.17), with both comparisons demonstrating statistical significance ($p < .05$). Yet no significant difference was found between the mean pretreatment HVLT Recall scores (43.65 ± 13.369) and posttreatment scores (39.94 ± 14.166). These results demonstrate improvement in participants' immediate verbal list recall performance at 1-month follow-up compared to pre- and posttreatment performance, but fail to demonstrate that bifrontal ECT caused impairment in immediate anterograde word list memory.

For the results of the delayed word list-learning memory test, a repeated measures ANOVA compared participant mean scores on the HVLT Delayed test across the three test administrations. Results of the ANOVA, seen above in Figure 2, revealed that participants' average HVLT Delayed scores differed significantly across the three test sessions, $F(2,30) = 11.455$, $p < .05$, $\eta_p^2 = 0.433$. Post-hoc analyses using the Bonferroni adjustment for significance indicated that the average HVLT-R Delayed scores were significantly higher at follow-up (49.75 ± 10.22) than the average scores prior to treatment (42.25 ± 13.73) and immediately after (42.25 ± 13.73). Pre- and posttreatment comparisons with follow-up scores showed statistically significant findings ($p < .05$). This is similar to the results from the HVLT Recall condition, which demonstrated that performance on average at follow-up was significantly improved from the performance pre and posttreatment. As with the immediate

condition, no statistically significant findings in terms of differences between the pre (42.25 ± 13.73) and posttreatment (42.25 ± 13.73) mean test scores, however, were shown indicating a lack of evidence that bifrontal ECT resulted in any impairments in delayed recall of a previously presented list of words repeatedly presented 25 minutes earlier.

Research Question 3

What are the effects of bifrontal ECT on participants' performance on measures of executive functioning immediately posttreatment and at 1-month follow-up? To address the question of the impact of bifrontal ECT on measures of executive functions, scores from the FAS verbal fluency test and several measures from the Behavioral Dyscontrol – Electronic Version were analyzed with repeated measures ANOVAs.

Table 8 displays the means and standard deviations from the FAS Verbal Fluency Test. As seen in Figure 3, the repeated measures ANOVA comparing mean FAS test scores among pretreatment, posttreatment, and follow-up revealed significant differences between the mean scores for the three administrations, $F(2,32) = 18.541$, $p < .05$, $\eta_p^2 = 0.537$. Post-hoc comparisons analyses using the Bonferroni adjustment for significance indicated that the average FAS scores were statistically significantly lower at posttreatment (5.59 ± 3.74) compared to pretreatment (9.88 ± 2.78, $p < .05$) and follow-up (9.41 ± 3.26, $p < .05$), but found no statistically significant differences between the mean FAS scores from pretreatment (9.88 ± 2.78) compared to follow-up

Table 8

Means and Standard Deviations at Pretreatment, Posttreatment, and Follow-up for the FAS test

	Pretreatment	Posttreatment	Follow-up
Mean FAS Scores (Standard Deviation)	9.88 (2.78)	5.59 (3.74)	9.41 (3.26)

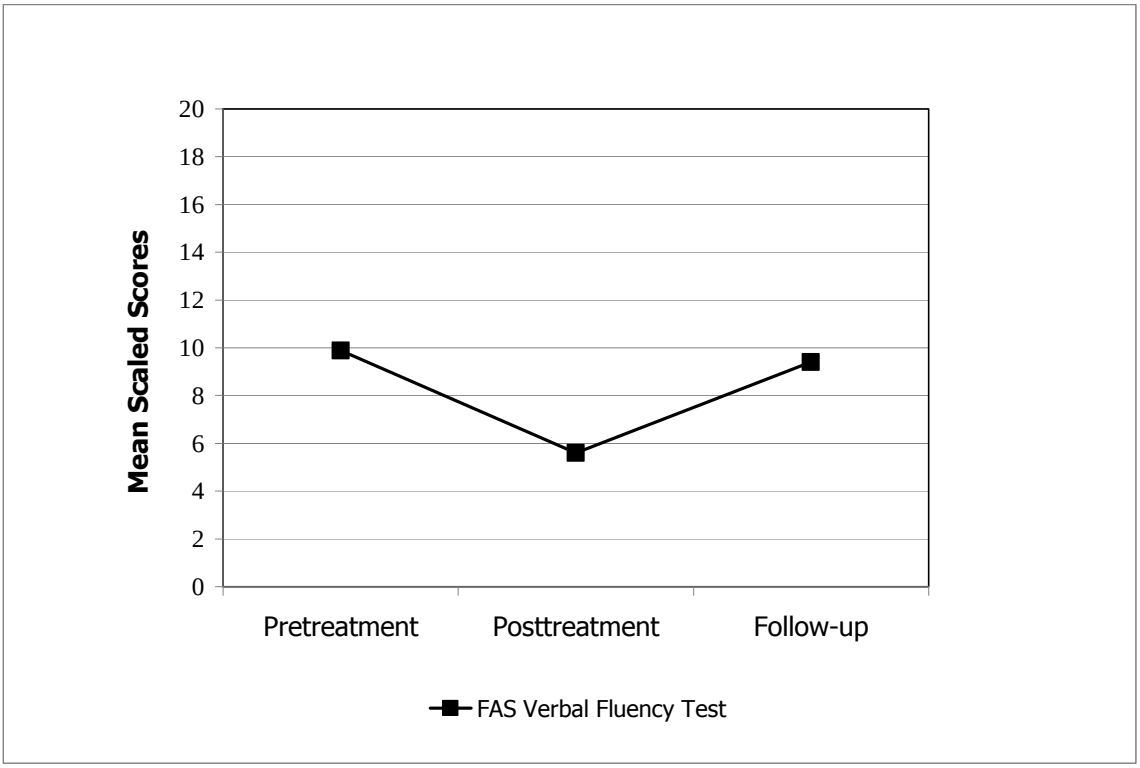

Figure 3. Group Comparison of Mean Scores from the FAS Verbal Fluency Test

* Average scaled scores range from 7-13 (standard deviation = 3)

(9.41 ± 3.26). This data pattern showed that, on average, there were significant reductions in verbal fluency scores immediately posttreatment; however, by the time of follow-up 1 month later, participant performance had, on average, returned to baseline. The findings indicate that in terms of verbal fluency, any negative side effects that occurred as a result of treatment appeared to be transient.

Results of the Alphanumeric sequencing test from the Behavioral Dyscontrol Scale – Electronic Version (BDS-EV) were used to evaluate the following components of executive functions: cognitive flexibility, information processing speed, visual scanning ability, integration of visual and motor functions, sequencing, and the ability to shift train of thought. Table 9 reports the means and standard deviations from the raw scores for total time to complete the Alphanumeric sequencing task.

As seen in Figure 4, a repeated measures ANOVA that compared participants' mean completion times on the Alphanumeric sequencing task across the three administrations did not indicate any differences in performance on this task between pretreatment, posttreatment, and follow-up. That is, there were no statistically significant changes in mean scores between pretreatment, posttreatment, and follow-up testing on this task. Total response time (the time it takes to formulate and execute a response) on the Simple choice reaction time (SCRT) tasks from the BDS-EV, was used to capture aspects of attention, motor planning, and motoric speed, also aspects of executive functioning. Individual

Table 9

Means and Standard Deviations at Pretreatment, Posttreatment, and Follow-up for the Alphanumeric Sequencing (ANS) Task

	Pretreatment	Posttreatment	Follow-up
Mean ANS Completion Time in Milliseconds (Standard Deviation)	35897.31 (8382.66)	46465.00 (20098.91)	42017.38 (16348.06)

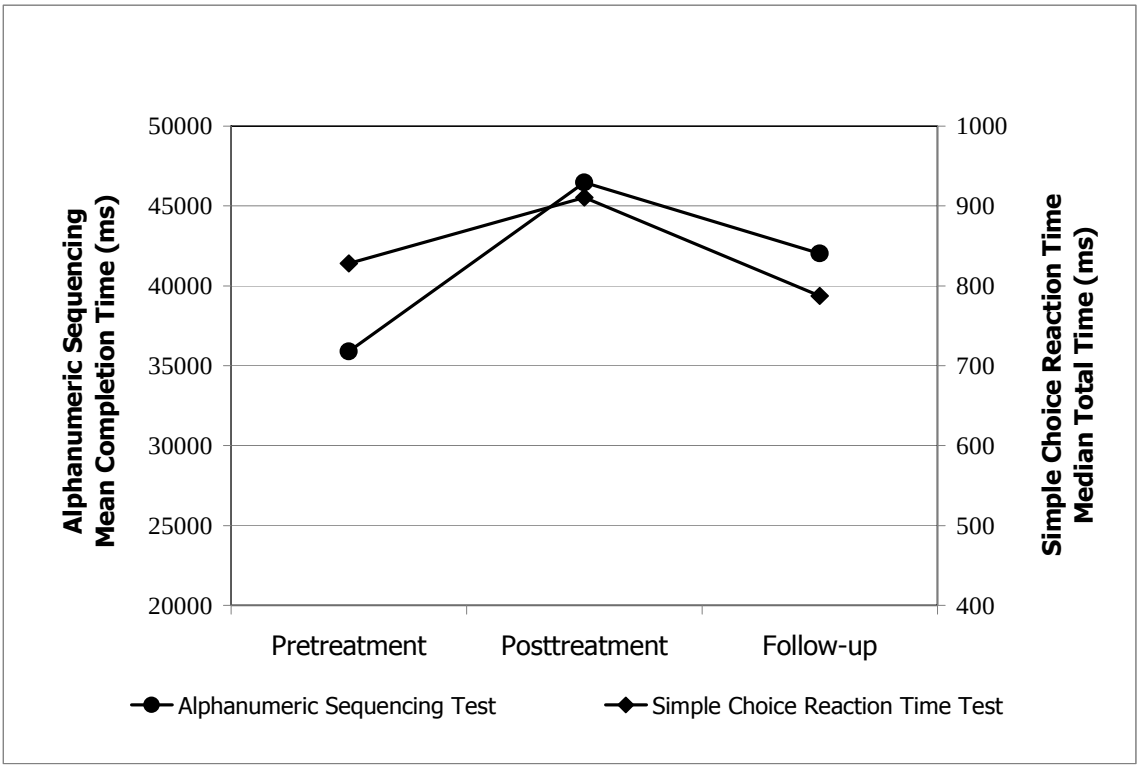

Figure 4. Group Comparison of Mean or Median Scores from the Alphanumeric Sequencing and Simple Choice Reaction Time Tasks

participant median total response time was calculated for the SCRT trials. Table 10 shows the means and standard deviations for participants' median total response time on the SCRT.

A repeated measures ANOVA, also illustrated in Figure 4, which compared the means for total response time per trial between pretreatment, posttreatment, and follow-up testing for the SCRT task, did not indicate a main effect of the treatment. There were no statistically significant differences in mean scores between pretreatment, posttreatment, and follow-up testing on this task suggesting that bifrontal ECT treatment did not result in changes in participant performance on average for this task.

The total number of errors from the Branching Go-No-Go (BGNG) task from the BDS-EV were analyzed to provide a measure of impulsivity in responding, another executive function thought to be mediated by frontal lobe activity. Table 11 reports the means and standard deviations for participants' total errors on the BGNG task.

As seen is Figure 5, a repeated measures ANOVA compared participants' mean total errors between pretreatment, posttreatment, and follow-up testing administrations and revealed that average errors differed significantly between the three test administrations, $F(2,26) = 5.423$, $p < .05$, $\eta_p^2 = 0.294$. Post-hoc analyses using the Bonferroni adjustment for significance indicated that the average number of errors on the BGNG task was statistically significantly lower at follow-up (1.29 ± 1.20) than at pretreatment (3.14 ± 3.21, $p < .05$).

Table 10

Means and Standard Deviations at Pretreatment, Posttreatment, and Follow-up for the Simple Choice Reaction Time (SCRT) Task

	Pretreatment	Posttreatment	Follow-up
Mean SCRT Total Time in Milliseconds (Standard Deviation)	828.21 (205.86)	910.68 (193.70)	787.50 (123.10)

Table 11

Means and Standard Deviations at Pretreatment, Posttreatment, and Follow-up for the Branching Go No Go (BGNG) Task

	Pretreatment	Posttreatment	Follow-up
Mean Errors for BGNG Task (Standard Deviation)	3.14 (3.21)	2.36 (3.10)	1.29 (1.20)

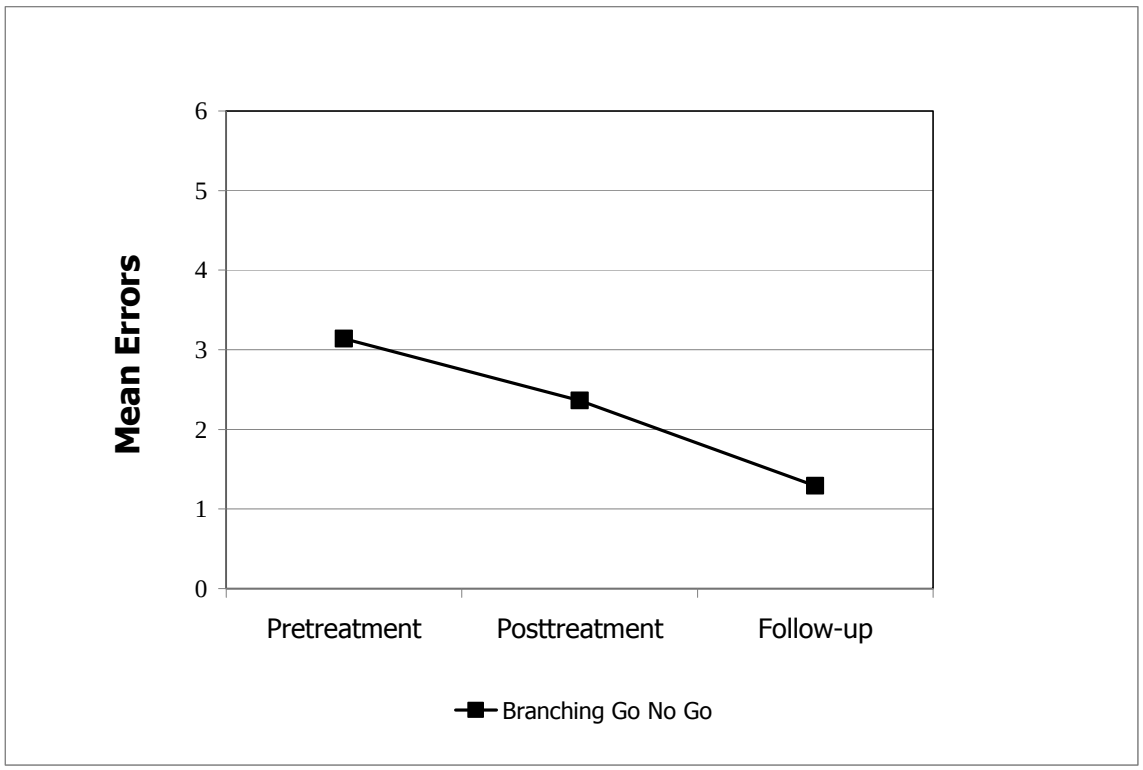

Figure 5. Group Comparison of Mean Errors
Made on the Branching Go-No-Go Task

Comparisons failed to demonstrate statistically significant differences between the mean number of errors made at pre- (3.14 ± 3.21) versus posttreatment (2.36 ± 3.10) or between posttreatment (2.36 ± 3.10) and follow-up (1.29 ± 1.20). This pattern of results suggests that participants displayed significantly less impulsivity in responding at follow-up compared to measures taken at baseline. From these results, we can conclude that the treatment resulted in an improvement in participants' ability to inhibit responding over the course of treatment.

Research Question 4

What are the effects of bifrontal ECT on participants' performance on measures of processing speed immediately posttreatment and at 1-month follow-up? To address this question regarding the impact of bifrontal ECT on measures of processing speed, the Processing Speed Index (PSI) scores (derived from the combination of the WAIS-III subtests of Digit-Symbol Coding and Symbol Search) were analyzed. Table 12 shows the means and standard deviations from the PSI.

As shown in Figure 6, a repeated measures ANOVA compared the mean participant PSI scores between pretreatment, posttreatment, and follow-up test administrations and revealed differences between the scores at the three test sessions, $F(2,30) = 7.854$, $p < .05$, $\eta_p^2 = 0.344$. Post-hoc analyses using the Bonferroni adjustment for significance indicated that the average PSI scores were significantly higher at follow-up (95.81 ± 12.92) than at posttreatment

Table 12

Means and Standard Deviations at Pretreatment, Posttreatment, and Follow-up for the Processing Speed Index (PSI)

	Pretreatment	Posttreatment	Follow-up
Mean PSI Scores (Standard Deviation)	91.06 (15.14)	85.13 (10.76)	95.81 (12.92)

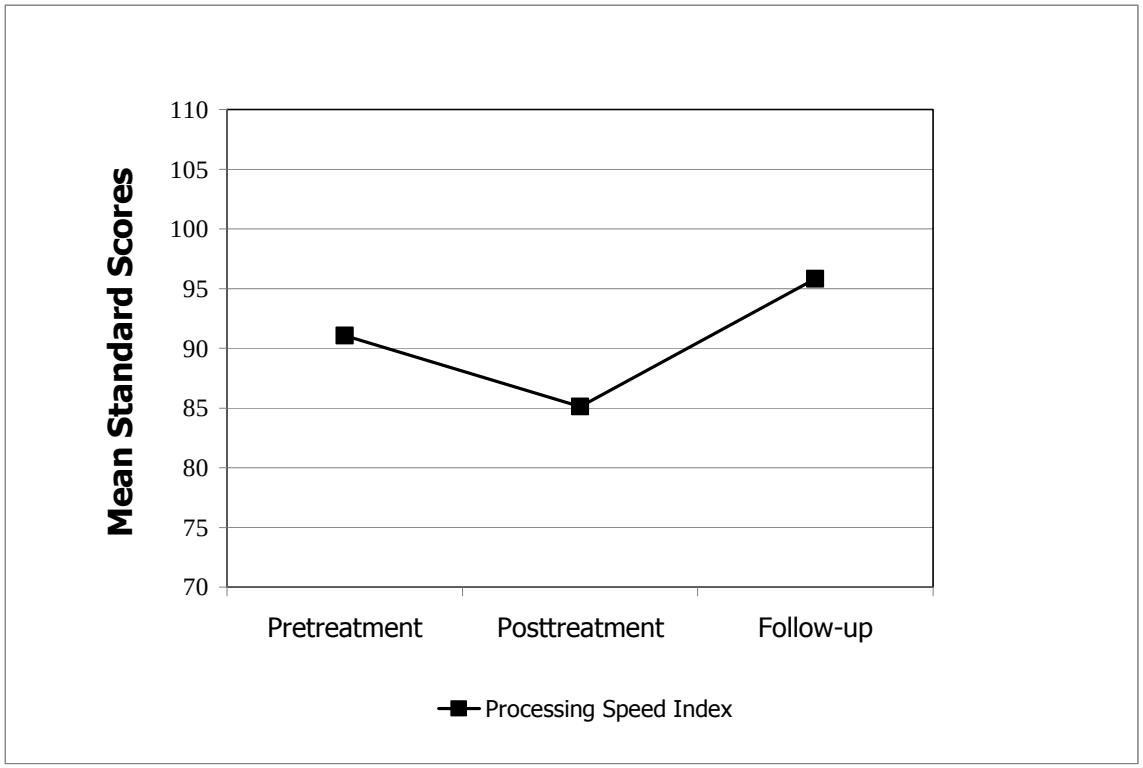

Figure 6. Group Comparison of Mean Scores on the Processing Speed Index

* Average standard scores range from 85-115 (standard deviation = 15)

(85.13 ±10.76, $p < .05$). Mean PSI scores decreased slightly from pretreatment (91.06 ± 15.14) to posttreatment (85.13 ±10.76), although this was not statistically significant. There was also no difference found between pretreatment PSI means (91.06 ± 15.14) and follow-up (95.81 ± 12.92). This pattern of results failed to demonstrate any ill effects of bifrontal ECT on processing speed, but instead, similar to measures of anterograde memory and impulsivity, suggests that participants displayed marked improvements in processing speed at 1-month follow-up.

Supplementary Analyses

The Mini-Mental Status Exam (MMSE) was administered to provide a direct comparison with previous bifrontal studies that relied solely on this test as their dependent measure of cognitive function. In the current study, results of a repeated measures ANOVA on the MMSE raw scores failed to show a main effect for cognitive change from bifrontal ECT treatment. This finding is consistent with those from several previous studies that demonstrated a lack of effect of bifrontal ECT on cognitive status (e.g., Bailine et al., 2000; Eschweiler et al., 2002; Heikman et al., 2002; Kellner et al., 2010; Ranjkesh et al., 2000; Schulze-Rauschenbach et al., 2005).

In an effort to capture participants' subjective opinions regarding memory functions across treatment, participants were given the opportunity to rate their memory ability before treatment was provided and after treatment (i.e., immediately following treatment and at the 1-month follow-up. Self-assessment

of memory functioning was done using a scale of 1 to 7, with 1 reflecting no perceived memory disturbances and 7 reflecting severe memory difficulties. Ten participants completed the subjective memory question at pretreatment and follow-up and 9 completed it immediately posttreatment. At pretreatment, the mean subjective memory rating was 3, with a range of scores from 1 to 5. Immediately posttreatment scores ranged from 1 to 6 with a mean of 3.45. At follow-up the mean rating was 4.6, with scores ranging from 2 to 7. Analyses of these results suggest that participants already perceived mild memory difficulties prior to treatment which did not change drastically at posttreatment, but by follow-up on average participants reported a slight increase in memory problems. Although not statistically significant, the results approach significance ($t(8) = -2.229$, $p = .056$), suggesting that participants demonstrated a trend toward reporting significantly greater problems with their memory by 1-month follow-up. These findings are consistent with previous findings of subjective memory complaints that persist even several months posttreatment (Squire & Slater, 1983).

Participants were also asked to rate how effective they considered bifrontal ECT in treating their depression. On a scale of 1 to 7, with 1 being completely ineffective and 7 being completely effective, the sample yielded an average effectiveness rating of 4.40 (SD=2.17). This suggests that, on average, the 10 participants who rated the effectiveness of bifrontal ECT considered it moderately effective. However, the scores ranged from 1 to 7, demonstrating

considerable difference in the perception of treatment effectiveness. A correlational analysis demonstrated a significant negative correlation between participants' ratings of the effectiveness of the ECT treatment and their HAM-D scores at follow-up ($r(8)=-.715$, $p<.05$). This suggests that as participants' levels of depressive symptoms rose their opinion of the effectiveness of their treatment decreased.

Finally, to determine necessary sample sizes to detect effects on the measures that did not yield significant ANOVA results power analyses were conducted. A power of .8 (80% probability of rejecting a false null) was used. For the MMSE, results of the power analysis suggested 1,313 participants would have been necessary to detect effects. Concerning the Logical Memory I and II tests power analyses revealed sample sizes of 141 and 41 participants, respectively, would have been necessary. Last, for the computer-administered tests, SCRT and ANS, power analyses suggested sample sizes of 50 and 62 would have been necessary to detect effects. Therefore, results suggest that participant sample sizes much larger than the 30 would have been necessary to detect effects. Small effect sizes rather than insufficient sample size may be to blame for the lack of significance with these measures.

CHAPTER 4

DISCUSSION

This study set out to examine the clinical efficacy and potential cognitive side effects of bifrontal ECT, an ECT variation that has received far less attention in the literature than bitemporal or right unilateral procedures. Further, the study aimed to compare current findings to those of previous research on other forms of ECT. Embedded in this effort is the concern that the mental cost (or side effects) of ECT may outweigh its potential benefits, especially if the treatment itself were to result in side effects that served to worsen or exacerbate an individual's depressive symptomatology. ECT research has long debated the risk/benefit ratio of electroconvulsive treatment and some have proposed that bifrontal ECT may result in a more favorable ratio (Heikman et al., 2002). Further, all ECT research shares the common goals of providing detailed specific information to potential patients concerning expected outcomes, both negative and positive, as well as informing decisions in clinical practice. Despite its limitations, which will be discussed below, this study represents a significant contribution to this discussion and builds upon the current empirical knowledge base concerning bifrontal ECT.

Major Research Findings

Treating Depression with Bifrontal ECT

Results of the present study indicate that bifrontal ECT is as effective a treatment of severe depression as other forms of ECT, and may have fewer side effects. The study showed that 88% of the participants responded immediately after completion of a standard series of bifrontal ECT, a rate that is comparable to the 70 to 90% response rate for all types of ECT reported by the American Psychiatric Association's (2010) practice guidelines regarding treatment for depression, and higher than remission rates of 55% and 64% found in multisite research consortium projects (Kellner et al., 2006; Sackeim et al., 2001). Clearly, bifrontal ECT can be considered an effective course of action for severe, medication-resistant, depressive conditions.

Like other investigations, the current study also found that a number of participants experienced a significant return of depressive symptoms 1 month after treatment cessation and that on average participants demonstrated an increasing trend in depression symptomatology from posttreatment to follow-up. Specifically, 13% of the participants who were shown to have a positive initial response (a 50% or more reduction in symptoms from pre- to posttreatment) were later classified as relapsed 1 month after the cessation of treatment, and all but 1 of the 15 participants initially considered responsive to treatment demonstrated an increase in their HAM-D scores from posttreatment to follow-up foreshadowing rising levels of depression.

Although the ideal goal is to prevent relapse, the 13% relapse rate found in this study is still relatively low compared to some other studies of ECT (such as Prudic et al., who reported a 64% 24-week relapse rate in their 2004 publication and Grunhaus et al., who reported a 28.5% 3-month relapse rate in their 2001 study).

The excitement that these data stir concerning very low relapse rates at follow-up must be tempered due to the lack of a longer follow-up period. This is considered a limitation of this study. The present data are restricted to only 1-month follow-up which is much shorter than the follow-up periods of 24 weeks from Prudic et al. and 3 months in Grunhaus et al. This provides reason to be cautious in making strong conclusions about bifrontal ECT relapse rates. It is plausible that given the trend in the current sample of rising symptomatology longer follow-up periods may have resulted in a higher relapse rate.

Effects of Bifrontal ECT on Memory

Memory loss and confusion represent the bulk of the complaints from individuals who have received ECT treatment (Malcolm, 1989; Squire & Slater, 1983). In its inception, bifrontal electrode placement was hypothesized to spare memory functions because it avoids direct stimulation over the temporal lobes (Inglis, 1969). Prior to the current study, only two previous studies (Kellner et al., 2010; Lawson et al., 1990) had attempted to assess memory functions in bifrontal ECT with targeted neuropsychological measures.

The present findings failed to corroborate the findings of Kellner et al.

(2010) concerning ill effects of bifrontal ECT on measures of verbal anterograde memory. Current results found no evidence of impaired anterograde memory on any of the measures administered, suggesting that bifrontal ECT did not result in impaired recall of newly learned information in this study. Specifically, concerning the ability to recall a story, no differences were found in participant performance between pretreatment, posttreatment, and follow-up. Further, contrary to the findings of Kellner et al. (2010), current results did not suggest impairment in immediate or delayed recall of information in learning a list of words. Rather, results of immediate and delayed tests of list learning were suggestive of average improvement at follow-up testing over pre and posttreatment performance. A possible interpretation of these results is that the relief of depression resulted in improved verbal memory functions by follow-up, while an alternative consideration is that the improvement is attributable to practice effects from repeated exposure to the list of words. The lack of alternative test forms is considered another limitation of the current study.

Unfortunately, like previous ECT findings (Kellner et al., 2010; Sackeim et al., 2007) the current study showed persistent problems with retrograde amnesia. Whether retrograde amnesia will persist beyond 1 month is unclear; however, data from other investigations, including that of Sackeim et al. (2007), suggest that by 6 months posttreatment, there may be substantial improvement in the ability to remember autobiographical information.

In this study, the results of the Autobiographical Memory Interview

revealed that bifrontal ECT had a significant impact on the accuracy of participants' memories of previously recalled personally relevant information. On average, participants remembered only 72% of the information provided at pretreatment interviews immediately following the completion of their series of ECT treatments. At 1-month follow-up they remembered 69%. Contrary to findings that ECT does not produce cognitive effects that persist after treatment cessation (Lawson et al., 1990) and the hypothesis that bifrontal ECT may spare memory functions (Inglis, 1969) these results suggest that memory of personally relevant biographical information is significantly compromised with bifrontal ECT treatment and persists at least 1 month posttreatment. These findings are consistent with those of Kellner et al. (2010) who demonstrated that all three electrode placements caused impairment on this measure. Kellner et al. further demonstrated that bifrontal ECT caused a slightly greater disturbance in autobiographical memory than bitemporal or right unilateral electrode placement. Specifically, Kellner et al. found that participants who received bifrontal ECT could remember only 58% of the information provided on the AMI at baseline, whereas the current study found average recall on the AMI of 72% immediately posttreatment. Therefore, the current results suggest slightly less impairment in retrograde amnesia for bifrontal ECT compared to Kellner et al. Findings by Kellner et al. of 69 and 67% retrograde amnesia scores for the right unilateral and bitemporal groups are more consistent with present findings. When integrated with the current results this suggests that retrograde amnesia levels

are quite similar across the three electrode placements.

Again, a lack of longer follow-up testing presents a limitation in interpreting this study's retrograde amnesia data. It remains unknown whether retrograde amnesia would persist indefinitely or would dissipate after more time.

Another limitation is that the AMI represents an imperfect measure of retrograde amnesia. For example, if participants offer inaccurate or vague memories during the pretreatment interview, that can confound their accuracy of recall at posttreatment and follow-up. Even though participants were encouraged to offer only clear and accurate memories, there was no mechanism to check accuracy. Since depression itself is believed to negatively affect memory and cognition (Calev et al., 1995), pretreatment responses could already be comprised by participants' depressed states. The accuracy of the measure could be improved by consulting with participants' families and friends to corroborate baseline responses, although if the individual has encoded the memory inaccurately, efforts to corroborate responses may confound the issue further. That said, the AMI is the most widely used measure of retrograde memory employed in ECT research. It likely represents the only standardized approach to measuring the autobiographical memory loss, which has long been a complaint of those who have completed ECT treatment (Rose et al., 2003).

Clearly, the current data and data from more recent studies of bifrontal ECT (Kellner et al., 2010), strongly suggest that this electrode placement does not spare all memory functions as was initially predicted (Inglis, 1969). Yet there

is no evidence, from current results, that bifrontal ECT causes greater memory impairment than alternative electrode placements.

Effects of Bifrontal ECT on Executive Functions

Executive functions refer to an individual's ability to plan, execute, generate, organize, inhibit, and modify goal directed behavior. These functions are predominantly controlled by the frontal lobe of the brain, the area where bifrontal ECT provides direct stimulation. Therefore, answering the question of whether bifrontal ECT causes impairment in executive functions is possibly the most important and novel contribution of this study. It provides one of the most thorough examinations to date of frontal lobe functions in ECT treatment.

The FAS verbal fluency test measures an individual's ability to generate verbal responses upon cueing under a time constraint. Results from this study are consistent with the findings from Calev et al. (1995) that bitemporal, right unilateral, and in this case bifrontal ECT, all result in impaired verbal fluency, although the ill effects of the treatment appear short-lived. Specifically, this study's participants generated significantly more words at pretreatment and follow-up than at posttreatment. Immediately posttreatment, mean scores on the FAS test fell from the average range to well below average (5th percentile), suggesting considerable functional impairment immediately posttreatment. On the positive side, mean scores returned to the average range by follow-up. This robust finding suggests that individuals undergoing bifrontal ECT may have clinically significant difficulty with verbal fluency and the generation of verbal

responses immediately following their treatment, but are likely to recover from these ill effects rather quickly. While Kellner et al. (2010) found no differences between the three electrode placements in letter or category fluency, their published data indicate that all three electrode placements resulted in comparable deterioration in category and word fluency as was found in this study.

Several computer-administered measures from the Behavioral Dystcontrol Scale – Electronic Version were employed to assess executive functions. The Alphanumeric sequencing (ANS) task is comparable to the popular Trails B task, a neuropsychological measure given in a paper-pencil format in several studies reviewed above (Kellner et al., 2010; Shulze-Rauschenbach et al., 2005). These tasks are considered measurements of cognitive flexibility, information processing speed, visual scanning ability, integration of visual and motor functions, sequencing, and the ability to maintain two different trains of thought. The unit of analysis for the ANS task was the total time participants took to complete the task. No differences were found in participants' performance speed between pretreatment, posttreatment, and follow-up assessments. This suggests no impact of bifrontal ECT on the performance of this task, consistent with the findings from Kellner et al. (2010). Interestingly, data from Kellner et al. demonstrated a trend toward improvement in completion speed for Trails B for all three electrode placements from pre- to posttreatment testing. Again, this improvement could be attributable to practice effects. Yet, despite repeated

exposure to the tasks in this study, no significant improvement between the three administrations was observed.

Total response time (a combination of decision and movement time) from the Simple choice reaction time (SCRT) task of the BDS-EV was used to capture aspects of attention, motor planning, and motoric speed, all considered executive functions. Decision speed refers to the time between the presentation of the stimulus on the screen and the point when the individual lifts his or her finger from the button indicating they have made a choice. Movement time captures the time elapsed between lifting their finger from the button and hitting the button corresponding to their choice. By analyzing these variables, we can get a sense for how long an individual takes to generate an answer, create a motor plan, and execute the movement. In this analysis, no impact of the treatment was observed. This was consistent with findings from Sackeim et al. (2007) who found no ill effects of bitemporal or right unilateral ECT on measures of simple reaction time.

Finally, errors from the Branching Go-No-Go task were analyzed to capture aspects of impulsivity versus inhibition in responding. This is an important aspect of executive functioning that previous studies have not addressed. In the present case, results suggested that impulsivity and inhibition improved as a result of treatment, as follow-up error scores were significantly lower than pretreatment error scores. This improvement could be hypothesized to result from the relief of depression, but the issue of practice effects must

again be considered. Participants completed the same task three times, which may have allowed for adjustment to the task demands from pretreatment to follow-up assessment administrations. Nevertheless, current results lack evidence that bifrontal ECT causes impairment in inhibition or impulsivity.

To summarize, it does appear that verbal fluency is adversely affected immediately following bifrontal ECT. Any ill effects appear to diminish quickly, and do not appear to impact functioning long-term. All other areas of executive function appear unaffected by bifrontal ECT treatment. These findings are consistent with those of Kellner et al. (2010), which suggested no disadvantage of bifrontal ECT on measures of executive functions when compared to other electrode placements. This is an extremely important finding, considering the hypothesis that executive functions could be adversely affected by bifrontal ECT.

Participant Experience with Bifrontal ECT

Historically, a challenge of ECT research has been to quantify subjective memory complaints of ECT patients. The current study employed a subjective question to target just this issue. In keeping with the findings of Squire and Slater (1983), current results suggested that individuals treated with bifrontal ECT tend to experience negative effects on memory that standardized measures often fail to capture. In this study, participants rated their memory as worse at follow-up than at pre- or posttreatment. Mean ratings rose from the low to the middle range of a seven-point subjective scale assessing participant experience of memory impairment. Statistical analyses did not find significant differences in

participants' average subjective memory ratings between any of the three testing sessions, but these results are still important in that they demonstrate a rising concern about memory functions across treatment. Further, they demonstrate that subjective complaints still exist and may contribute to the fear and stigma associated with ECT treatment.

Participants were also asked to rate how effective they considered bifrontal ECT in treating their depression. Interestingly, participant responses ranged from completely ineffective (a rating of 1) to completely effective (a rating of 7) with the average falling in the moderately effective range and suggesting that participants differed significantly in their individual perceptions of treatment effectiveness. As would be predicted, there was a moderately strong negative correlation (r=-.715, p<.05) between effectiveness ratings and follow-up HAM-D interview results such that participants experiencing more depressive symptoms at follow-up rated the effectiveness of ECT treatment lower. This speaks to a flaw in the design of the study, as this question appears to capture more about how the participant is feeling at the time of follow-up rather than the participant's perception of ECT's effectiveness across their entire treatment course. Future studies wishing to assess patient opinion about effectiveness may wish to capture this at posttreatment as well as follow-up, given that ECT appears to be more effective immediately following treatment compared to weeks or months after cessation.

Specificity of Measures in ECT Research

The Mini-Mental Status Exam is the most commonly used cognitive measurement in ECT research, and has often served as the sole measure of cognitive effects in studies (Bailine et al., 2000; Eschweiler et al., 2007; Heikman et al., 2002; Ranjkesh, Barekatain, & Akuchakin, 2005). The MMSE was also included in the battery of tests given in the current study for purpose of comparison. Results demonstrated no significant changes in MMSE scores between pretreatment, posttreatment, and follow-up assessments. Interestingly, a power analysis set at level .8 showed that 1,313 participants would have been necessary to find significant effects with this measure. This suggests that the lack of significance in MMSE results is probably not the result of small sample size. Rather, it is more likely due to a miniscule effect, detection of which would require a very large sample. These results call into question the results of prior ECT studies that employed the MMSE as the only measure of cognitive functioning. Based solely on results from the MMSE, many studies have drawn sweeping conclusions about the effects of ECT on cognition.

This finding serves to remind consumers of ECT research and those who design ECT studies of the importance of including comprehensive neuropsychological measures. Without comprehensive measures, such as those employed in the current study, conclusions about the cognitive side effects of ECT appear significantly compromised.

Procedural Considerations and Limitations

A significant procedural consideration involves the lack of random assignment and a control group in this study. The failure to randomize participants and the resulting possibility of a self-selection bias for ECT over alternative treatments for depression may reduce the generalizability of the results. Inclusion of random assignment and comparison and control groups could increase the strength of future bifrontal ECT studies.

The administration of maintenance ECT treatments to participants, although a common clinical practice following ECT treatment utilized to reduce relapse (Kellner et al., 2006; Sackeim et al., 2001), is also considered a minor limitation of this study. Following the completion of their standard series of bifrontal ECT, and during the time between the posttreatment and follow-up neuropsychological assessments, 8 of the 17 participants received maintenance ECT treatments. Four individuals received one maintenance treatment between posttreatment testing and follow-up, 3 received two maintenance treatments, and 1 individual received seven maintenance treatments between post and follow-up testing.

Interestingly, the participant who received the largest number of maintenance treatments (seven) displayed the greatest reduction in AMI scores, recalling only 59% and 38% of initial AMI responses at posttreatment and follow-up. Similarly, at follow-up, this individual also displayed the lowest FAS verbal fluency score of all the participants. Otherwise, visual analyses of the

other measures appear to reflect the similar trends seen in the statistical analyses of the full study sample. These results, although based solely on visual analysis of one individual's scores, could suggest a cumulative negative effect of ECT treatment on retrograde amnesia and verbal fluency, an area worthy of exploration in future ECT research.

Since nearly half the study participants received intervening maintenance ECT treatments, one could suspect that the scores at follow-up might have been adversely affected. However, since few measures demonstrated evidence of impairment, the effects of these maintenance treatments appear negligible. This strengthens the hypothesis that ECT causes few measurable changes in cognition. On the positive side, maintenance treatments are commonly used in clinical and community-based ECT programs (those conducted outside randomized controlled clinical trials), and their inclusion in this study provides an investigation of ECT treatment that better approximates common clinical practices and increases the generalizability of the results.

Clearly larger sample sizes are preferred, as they increase generalizability and may improve statistical power. The small sample size of 17 in this study represents a limitation. Yet, the majority of the test measures in the analyses revealed statistically significant ANOVA omnibus effects. Power analyses of those measures that failed to yield significant effects suggested small sample size was not to blame. Rather, the effects themselves appear miniscule, requiring very large sample sizes (as was discussed above with the MMSE) in order to detect

significant findings. Still, larger sample size would add more variability, which in turn strengths generalizability.

Another limitation of the current study involves the reliability of the administration of the HAM-D. In most ECT studies with larger samples, raters reached a sufficient level of reliability on the administration of the HAM-D, typically ranging from .8 to .9. In the current study, the main study psychiatrist initially administered the HAM-D. But after training by an independent psychiatrist, the primary investigator administered the majority of the HAM-D interviews. This was done to avoid bias, since the study psychiatrist had substantial prior knowledge of participants' history and clinical presentation. When questions surfaced concerning HAM-D scoring, the primary investigator would consult with the study psychiatrist until they agreed on the rating. However, no HAM-D administrations were repeated to reach a specified level of reliability.

A final limitation is the possibility of practice effects due to the lack of alternative forms for several test measures, including story memory, word list learning, verbal fluency, processing speed, and all computerized measures of executive functions. Kellner et al. (2010) did not use alternative forms either, yet their findings suggested that bifrontal ECT participants demonstrated anterograde amnesia for list learning despite repeated exposures to the same list. In the current study it is possible that increased competence due to practice effects may have masked possible impairment on these measures. When

possible, future bifrontal ECT studies should consider using alternative measurement forms to reduce the impact of practice effects and more clearly differentiate the effects of bifrontal ECT on cognition.

Implications

Data from the current study contribute to the evidence base that examines the effectiveness of bifrontal ECT for treating severe unipolar and bipolar depression. The current study demonstrated much higher ECT responsiveness and lower relapse rate than previous studies conducted outside the context of randomized controlled clinical trials. These are extremely important findings, in that they establish bifrontal ECT as an equally effective treatment for severe depression as other electrode placements. Furthermore, these results are derived from an authentic clinical ECT treatment program, and despite a small sample size, conclusions may generalize to similar university-based hospital treatment programs.

Concerning cognitive side effects, the current data call into question the hypotheses that bifrontal ECT may result in impaired executive functions due to direct stimulation of the frontal lobes. This study provides a significant contribution to the very limited research base examining executive functioning with bifrontal ECT and suggests that executive functions may not be ill affected by bifrontal stimulation. Unfortunately, despite hypotheses that bifrontal ECT might spare memory functions because it avoids stimulation to the temporal lobes, current findings suggest that bifrontal ECT, like other electrode

placements, may cause impairment in retrograde autobiographical memory. Further, data show that bifrontal ECT likely results in significant difficulty with verbal fluency immediately posttreatment. Although this effect appears short-lived, this may cause distress in individuals who receive bifrontal ECT. Yet, current findings failed to demonstrate any ill effects of bifrontal ECT on anterograde memory or in any other area of cognition.

Future Research Directions

Although participants in this study served as their own controls due to the repeated measures design, future research on bifrontal ECT may be strengthened by including control and comparison treatment groups and employing random assignment. Data from a nondepressed control group may prove helpful, specifically on the Autobiographical Memory Interview, to illuminate the extent to which inaccurate recall of events is due to the passage of time or the poor specificity of the measure itself.

The current study represents a preliminary effort to determine the effectiveness and cognitive side effects of bifrontal ECT. It would be helpful if future studies build upon this work by extending follow-up timelines and repeating neuropsychological measures at intervals such as 6 months, 1 year, or 2 years at follow-up. This would allow for an investigation of persistent retrograde amnesia after cessation of ECT treatment.

Further, it might be helpful to conduct studies that compared bifrontal ECT with other treatments, including those that hold promise for more rapid

symptom reduction without cognitive side effects. Isoflurane anesthesia is one example of such a treatment. A number of studies conducted in Europe found rapid antidepressant effects for repeated Isoflurane treatments without any cognitive side effects (Englehard, Carl, & Hartung, 1993; Langer, Neumark, Koinig et al., 1985; Langer et al., 1995).

Concerning the neuropsychological test battery, future bifrontal ECT studies may wish to include measures of visual anterograde and retrograde memory. The investigation of memory problems following bifrontal ECT in this study was limited only to verbal memory, leaving questions about the nature of visual memory problems with bifrontal ECT.

The distinction between efficacy in community ECT treatment programs versus those affiliated with ECT research programs has been emphasized in the literature. Specifically, the American Psychiatric Association (2010) reports much higher efficacy of ECT within the context of randomized controlled clinical trials (70-90%) than has been demonstrated in community settings (30-64%; Kellner et al., 2006; Prudic et al., 2004; Sackeim et al., 2001). Interestingly, the current study was conducted in a university-affiliated psychiatric hospital but outside the context of a randomized controlled clinical trial, yet demonstrated a remission rate of 88% immediately posttreatment. This highlights the need for thorough investigations of the variables that contribute to the efficacy of an ECT treatment program including physician/patient relationship, technical procedures, and electrode placement. Continued research in these areas could potentially improve

treatment outcomes in community hospital or clinic ECT programs and improve patient response in those settings.

Conclusions

These results help clarify to a great extent what patients can expect to experience following a treatment series with bifrontal ECT. In weighing the benefits versus the risks, these data strongly suggest the benefits are substantial in reducing the acute symptoms of depression while sparing cognition in most areas except autobiographical memory and immediate posttreatment verbal fluency.

Clearly delineating for patients what the risks are concerning cognitive side effects of bifrontal ECT may assist medical providers and potential patients enter into more informed decisions about their care. Providing this knowledge upfront may serve to greatly reduce an individual's anxiety and fear prior to bifrontal ECT treatment. Subsequently these results may help reduce the stigma of ECT, making it more likely to be utilized as a treatment option for severe, treatment-resistant depression.

APPENDIX A

CONSENT FORMS

Consent and Authorization Document

Background

You are being invited to take part in a research study conducted by researchers from the Departments of Psychiatry, Anesthesiology, Psychology and Neurology, University of Utah. Before you decide if you want to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you want to volunteer to take part in this study.

One of the standard medical treatments for moderate to severe clinical depression is Electroconvulsive Therapy (ECT), also known as "shock treatment". These ECT treatments are administered by physicians together with relaxant drugs and anesthetic medications and other therapeutic procedures as your physicians may in their judgment determine to be necessary or appropriate. ECT treatments are usually repeated at intervals, usually every 2-3 days for about 2.5 to 3.5 weeks and about 8 total treatments. In many cases, a series of ECT treatments leads to substantial improvement in symptoms of depression. We are investigating whether symptoms of depression can be equally improved by a different course of treatments involving no shocks. Instead the patient is simply put deeply to sleep with the inhalant anesthetic, Isoflurane, for the same series of 8 treatment sessions over the same 2.5 to 3.5 weeks. We will also test whether the Isoflurane treatments may have less side effects than ECT in terms of temporary memory problems. In other research studies, a small number of depressed patients have shown good results after Isoflurane anesthesia. Your physician and the physicians involved in this study believe that you are an appropriate candidate for either ECT or Isoflurane treatments.

Randomized and Blinded Trial

This research project is designed to compare Isoflurane treatments vs. ECT treatments in 50 patients with depression. In this initial Phase 1 of the study, 7-9 patients will be selected to receive Isoflurane as their treatment type while another 7-9 will be assigned to receive ECT. Before, during and after the treatments, you will have your depressive symptoms measured along with various aspects of memory and other cognitive functions. Some of the doctors involved will be blinded and they will not know which of the treatments you are receiving, while other doctors administering the treatments will know.

Study Procedure

Screening: During screening, you will be asked questions about your health history, medication use, and current health issues, with specific attention to your depressive symptoms including any thoughts you might have of suicide or self harm. We will also perform baseline or pretreatment tests of memory and mental function (total screening assessment time around 1 hour).

Treatments: Treatment procedures will take place at the University of Utah Neuropsychiatric Institute in the ECT Procedure Room. Each session is expected to take between 1.5 and 2.5 hours. If you are randomized to receive the standard ECT treatments, you will first be given the usual methohexital anesthesia and then a tourniquet will be placed around your wrist. Other medications will be given to reduce any excessive muscle contractions and other possible effects of the ECT stimulus. Then, the ECT stimulus will be administered and your physiological responses and vital signs will be monitored by your electroencephalogram (EEG), your electrocardiogram (ECG),

blood pressure, pulse oximetry and exhaled CO2 to assess your state of respiration and blood oxygen, anesthetic concentration, and by the evidence of muscle contraction in the hand with the tourniquet.
If you receive the Isoflurane anesthesia treatments instead of ECT, methohexital anesthesia will first be given, followed by inhaled Isoflurane just sufficient to suppress bursts in the monitored EEG tracing for approximately 15 minutes, and then anesthetic will be discontinued. Additional medications will be given to help reduce risk of nausea or vomiting. The total time for each treatment session is expected to be about 1.5 to 2.5 hours.
Whether you are assigned to receive ECT or Isoflurane, the treatments will be repeated 8 times over a 2.5 to 3.5 week period.

Assessing Changes in Depressive Symptoms, Memory and Cognition
The same tests of memory and mental function performed at baseline prior to the treatments will be repeated 12-24 hours after the 8th treatment and 4 weeks after the 8th and final treatment. Changes in severity of depressive symptoms will be assessed by a clinical interview before each of the 8 treatment sessions, as well as 24 hours after the last treatment session and at 4 weeks after the last treatment session.

Risks: ECT is a well established treatment procedure. Under the current standard of practice the significant risks of ECT include: short and long term memory impairment, status epilepticus and complications from anesthesia including life-threatening cardiac arrhythmias, respiratory arrest, myocardial infarction, stroke and even death. The physicians involved in these procedures are experienced with ECT and will be closely monitoring responses to the ECT and all vital functions, and will take all appropriate steps to minimize these risks.

Isoflurane is a standard anesthesia induction agent. Its use has been shown to be effective in standard surgical care. However, anesthesia carries the risk of complications including life-threatening cardiac arrhythmias, respiratory arrest, myocardial infarction, stroke and even death. The physicians involved in these procedures are experienced with Isoflurane anesthesia and will be closely monitoring responses to the treatment and all vital functions, and will take all appropriate steps to minimize these risks. Additional use of an oropharyngeal or laryngeal mask airway may be considered as necessary to ensure safe ventilation. Endotracheal intubation will be considered only as indicated by anesthetic pre-procedure evaluation and will be discussed with you prior to treatment. With the Isoflurane treatments, there is an additional risk that it may be ineffective in treating the patient's psychiatric illness resulting in worsening depression and potential prolongation of the patient's illness. The physicians involved in the study will be monitoring depressive symptoms at frequent intervals, and will minimize this risk by stopping the Isoflurane treatments and switching to the standard ECT treatments if symptoms worsen significantly.

REPRODUCTIVE RISKS
While ECT is currently indicated for the treatment for some psychiatric illnesses during pregnancy, the effects of deep Isoflurane anesthesia on the embryo or fetus are currently unforeseeable. It is possible that if the treatment is given to a pregnant woman it will harm the unborn child. Pregnant women must not take part in this study, nor should women who plan to become pregnant during the study. Women who are at risk of pregnancy will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. If you could become pregnant you must use an effective contraceptive during the course of this study. Acceptable methods of birth control

include abstinence, oral contraceptives, the contraceptive patch, the contraceptive ring, condoms, etc. If you become pregnant while taking part in the study, you must immediately tell your research doctor. Options will be discussed with you at that time. Whether or not you remain on study treatment, we will follow the outcome of your pregnancy and we will continue to follow you according to the study plan.

Unforeseeable Risks
In addition to the risks listed above, there may be risks which are currently unforeseen.

Benefits: ECT is a well established treatment procedure with decades of proven benefit for treating serious psychiatric illness such as psychotic depression, mania and suicidal thoughts. For many patients ECT is the most effective form of treatment for their illness and results in a return of mental health. Isoflurane treatments have limited research showing efficacy equal to ECT in severe psychiatric illness. However, if further studies demonstrate that Isoflurane is as effective as ECT in treating moderate to severe depression with less memory side effects, and no social stigma, it may offer depressed patients and their physicians a new treatment option that many might prefer.

Alternative Procedures
If you do not want to take part in the study, you may choose to not participate in this study. This will in no way affect the treatment you receive from your medical providers.

Confidentiality
We will keep all research records that identify you private to the extent allowed by law. Records about you will be kept locked in filing cabinets or on computers protected with passwords. Only those who work with this study will be allowed access to your information. However, representatives from the Food and Drug Administration, the National Institutes of Health and the National Alliance for Research on Schizophrenia and Affective Disorders (the sponsor) may inspect and/or copy the records that identify you. Results of the study may be published; however, your name and other identifying information will be kept private.

Person to Contact
If you have questions, complaints or concerns about this study, or if you think you may have been injured from being in this study, you can contact Dr. Howard Weeks at 801-583-2500. Dr. Weeks can be reached at this number 24 hours a day.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

Institutional Review Board
Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Related Injury Section
If you are injured from being in this study, medical care is available to you at the University of Utah, as it is to all sick or injured people. The University of Utah does not have a program to pay you if you are hurt or have other bad results from being in the study. The costs for any treatment or hospital care would be charged to you or your insurance company (if you have insurance), to the study sponsor or other third party (if

applicable), to the extent those parties are responsible for paying for medical care you receive. Since this is a research study, some health insurance plans may not pay for the costs.

The University of Utah is a part of the government. If you are injured in this study, and want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Utah Governmental Immunity Act is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See Section 63G-7-101 to-904 of the Utah Code.

Voluntary Participation
It is up to you to decide whether or not to take part in this research. If you do decide to take part you will be asked to sign this consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the relationship you have with the investigator or staff nor standard of care you receive.

Unforeseeable Risks
In addition to the risks listed above, there may be risks which are currently unforeseen.

Right of Investigator to Withdraw
You may withdraw from the study at any time without penalty. Dr. Weeks or Dr. Smith can withdraw you without your approval. Possible reasons for investigator withdrawal include significant worsening of depressive symptoms or evidence of intolerance to the treatment.

Costs to Participants and Compensation
There are no costs to you or any compensation for any of the procedures described above. However, if you are assigned to the conventional ECT treatment, and you have medical insurance coverage, we will bill your provider for these treatment costs in the ordinary manner.

New Information:
Sometimes new information about the topic being studied becomes available during a research project. If this happens, your research doctor will tell you about it so you can decide whether or not to continue.

Number of Participants
We expect about 50 people will be in this study.

Authorization for Use of Your Protected Health Information
Signing this document means you allow us, the researchers in this study, and others working with us to use information about your health for this research study. You can choose whether or not you will participate in this research study. However, in order to participate you have to sign this consent and authorization form.

This is the information we will use:

- Name, address, and telephone number
- Medical history including psychiatric symptoms, current and past medications or therapies
- Information from the memory testing

- Information on changes in your psychiatric symptoms that occur over the testing period

Others who will have access to your information for this research project are the University's Institutional Review Board (the committee that oversees research studying people) and authorized members of the University of Utah workforce who need the information to perform their duties (for example: to provide treatment, to ensure integrity of the research, and for accounting or billing matters).

If we share your information with anyone outside the University of Utah Health Sciences you will not be identified by name, social security number, address, telephone number, or any other information that would directly identify you, unless required by law.

You may revoke this authorization. This must be done in writing. You must either give your revocation in person to the Principal Investigator or the Principal Investigator's staff, or mail it to: Dr. Howard Weeks 501 Chipeta Way, Salt Lake City, Utah 84108. If you revoke this authorization, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research. This authorization lasts until this study is finished.

Consent
I confirm that I have read and understand this consent and authorization document and have had the opportunity to ask questions. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. I will be given a signed copy of the consent and authorization form to keep.

I agree to participate in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

_____
Participant's Name

_____ _____
Participant's Signature Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

Consent and Authorization Document

Background

You are being invited to take part in a research study conducted by researchers from the Departments of Psychiatry, Anesthesiology, Psychology and Neurology, University of Utah. Before you decide if you want to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you want to volunteer to take part in this study.

One of the standard medical treatments for moderate to severe clinical depression is Electroconvulsive Therapy (ECT), also known as "shock treatment". These ECT treatments are administered by physicians together with relaxant drugs and anesthetic medications and other therapeutic procedures as your physicians may in their judgment determine to be necessary or appropriate. ECT treatments are usually repeated at intervals, usually every 2-3 days for about 2.5 to 3.5 weeks and about 8 total treatments. In many cases, a series of ECT treatments leads to substantial improvement in symptoms of depression. We are investigating whether symptoms of depression can be equally improved by a different course of treatments involving no shocks. Instead the patient is simply put deeply to sleep with the inhalant anesthetic, Isoflurane, for the same series of 8 treatment sessions over the same 2.5 to 3.5 weeks. We will also test whether the Isoflurane treatments may have less side effects than ECT in terms of temporary memory problems. In other research studies, a small number of depressed patients have shown good results after Isoflurane anesthesia. Your physician and the physicians involved in this study believe that you are an appropriate candidate for either ECT or Isoflurane treatments.

Randomized and Blinded Trial

This research project is designed to compare Isoflurane treatments vs. ECT treatments in 50 patients with depression. In this initial Phase 1 of the study, 7-9 patients will be selected to receive Isoflurane as their treatment type while another 7-9 will be assigned to receive ECT. Before, during and after the treatments, you will have your depressive symptoms measured along with various aspects of memory and other cognitive functions. Some of the doctors involved will be blinded and they will not know which of the treatments you are receiving, while other doctors administering the treatments will know.

Study Procedure

Screening: During screening, you will be asked questions about your health history, medication use, and current health issues, with specific attention to your depressive symptoms including any thoughts you might have of suicide or self harm. We will also perform baseline or pretreatment tests of memory and mental function (total screening assessment time around 1 hour).

Treatments: Treatment procedures will take place at the University of Utah Neuropsychiatric Institute in the ECT Procedure Room. Each session is expected to take between 1.5 and 2.5 hours. If you are randomized to receive the standard ECT treatments, you will first be given the usual methohexital anesthesia and then a tourniquet will be placed around your wrist. Other medications will be given to reduce any excessive muscle contractions and other possible effects of the ECT stimulus. Then, the ECT stimulus will be administered and your physiological responses and vital signs will be monitored by your electroencephalogram (EEG), your electrocardiogram (ECG),

blood pressure, pulse oximetry and exhaled CO2 to assess your state of respiration and blood oxygen, anesthetic concentration, and by the evidence of muscle contraction in the hand with the tourniquet.
If you receive the Isoflurane anesthesia treatments instead of ECT, methohexital anesthesia will first be given, followed by inhaled Isoflurane just sufficient to suppress bursts in the monitored EEG tracing for approximately 15 minutes, and then anesthetic will be discontinued. Additional medications will be given to help reduce risk of nausea or vomiting. The total time for each treatment session is expected to be about 1.5 to 2.5 hours.
Whether you are assigned to receive ECT or Isoflurane, the treatments will be repeated 8 times over a 2.5 to 3.5 week period.

Assessing Changes in Depressive Symptoms, Memory and Cognition
The same tests of memory and mental function performed at baseline prior to the treatments will be repeated 12-24 hours after the 8th treatment and 4 weeks after the 8th and final treatment. Changes in severity of depressive symptoms will be assessed by a clinical interview before each of the 8 treatment sessions, as well as 24 hours after the last treatment session and at 4 weeks after the last treatment session.

Risks: ECT is a well established treatment procedure. Under the current standard of practice the significant risks of ECT include: short and long term memory impairment, status epilepticus and complications from anesthesia including life-threatening cardiac arrhythmias, respiratory arrest, myocardial infarction, stroke and even death. The physicians involved in these procedures are experienced with ECT and will be closely monitoring responses to the ECT and all vital functions, and will take all appropriate steps to minimize these risks.

Isoflurane is a standard anesthesia induction agent. Its use has been shown to be effective in standard surgical care. However, anesthesia carries the risk of complications including life-threatening cardiac arrhythmias, respiratory arrest, myocardial infarction, stroke and even death. The physicians involved in these procedures are experienced with Isoflurane anesthesia and will be closely monitoring responses to the treatment and all vital functions, and will take all appropriate steps to minimize these risks. Additional use of an oropharyngeal or laryngeal mask airway may be considered as necessary to ensure safe ventilation. Endotracheal intubation will be considered only as indicated by anesthetic pre-procedure evaluation and will be discussed with you prior to treatment. With the Isoflurane treatments, there is an additional risk that it may be ineffective in treating the patient's psychiatric illness resulting in worsening depression and potential prolongation of the patient's illness. The physicians involved in the study will be monitoring depressive symptoms at frequent intervals, and will minimize this risk by stopping the Isoflurane treatments and switching to the standard ECT treatments if symptoms worsen significantly.

REPRODUCTIVE RISKS
While ECT is currently indicated for the treatment for some psychiatric illnesses during pregnancy, the effects of deep Isoflurane anesthesia on the embryo or fetus are currently unforeseeable. It is possible that if the treatment is given to a pregnant woman it will harm the unborn child. Pregnant women must not take part in this study, nor should women who plan to become pregnant during the study. Women who are at risk of pregnancy will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. If you could become pregnant you must use an effective contraceptive during the course of this study. Acceptable methods of birth control

include abstinence, oral contraceptives, the contraceptive patch, the contraceptive ring, condoms, etc. If you become pregnant while taking part in the study, you must immediately tell your research doctor. Options will be discussed with you at that time. Whether or not you remain on study treatment, we will follow the outcome of your pregnancy and we will continue to follow you according to the study plan.

Unforeseeable Risks
In addition to the risks listed above, there may be risks which are currently unforeseen.

Benefits: ECT is a well established treatment procedure with decades of proven benefit for treating serious psychiatric illness such as psychotic depression, mania and suicidal thoughts. For many patients ECT is the most effective form of treatment for their illness and results in a return of mental health. Isoflurane treatments have limited research showing efficacy equal to ECT in severe psychiatric illness. However, if further studies demonstrate that Isoflurane is as effective as ECT in treating moderate to severe depression with less memory side effects, and no social stigma, it may offer depressed patients and their physicians a new treatment option that many might prefer.

Alternative Procedures
If you do not want to take part in the study, you may choose to not participate in this study. This will in no way affect the treatment you receive from your medical providers.

Confidentiality
We will keep all research records that identify you private to the extent allowed by law. Records about you will be kept locked in filing cabinets or on computers protected with passwords. Only those who work with this study will be allowed access to your information. However, representatives from the Food and Drug Administration, the National Institutes of Health and the National Alliance for Research on Schizophrenia and Affective Disorders (the sponsor) may inspect and/or copy the records that identify you. Results of the study may be published; however, your name and other identifying information will be kept private.

Person to Contact
If you have questions, complaints or concerns about this study, or if you think you may have been injured from being in this study, you can contact Dr. Howard Weeks at 801-583-2500. Dr. Weeks can be reached at this number 24 hours a day.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

Institutional Review Board
Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Related Injury Section
If you are injured from being in this study, medical care is available to you at the University of Utah, as it is to all sick or injured people. The University of Utah does not have a program to pay you if you are hurt or have other bad results from being in the study. The costs for any treatment or hospital care would be charged to you or your insurance company (if you have insurance), to the study sponsor or other third party (if

applicable), to the extent those parties are responsible for paying for medical care you receive. Since this is a research study, some health insurance plans may not pay for the costs.

The University of Utah is a part of the government. If you are injured in this study, and want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Utah Governmental Immunity Act is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See Section 63G-7-101 to-904 of the Utah Code.

Voluntary Participation
It is up to you to decide whether or not to take part in this research. If you do decide to take part you will be asked to sign this consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the relationship you have with the investigator or staff nor standard of care you receive.

Unforeseeable Risks
In addition to the risks listed above, there may be risks which are currently unforeseen.

Right of Investigator to Withdraw
You may withdraw from the study at any time without penalty. Dr. Weeks or Dr. Smith can withdraw you without your approval. Possible reasons for investigator withdrawal include significant worsening of depressive symptoms or evidence of intolerance to the treatment.

Costs to Participants and Compensation
There are no costs to you or any compensation for any of the procedures described above. However, if you are assigned to the conventional ECT treatment, and you have medical insurance coverage, we will bill your provider for these treatment costs in the ordinary manner.

New Information:
Sometimes new information about the topic being studied becomes available during a research project. If this happens, your research doctor will tell you about it so you can decide whether or not to continue.

Number of Participants
We expect about 50 people will be in this study.

Authorization for Use of Your Protected Health Information
Signing this document means you allow us, the researchers in this study, and others working with us to use information about your health for this research study. You can choose whether or not you will participate in this research study. However, in order to participate you have to sign this consent and authorization form.

This is the information we will use:

- Name, address, and telephone number
- Medical history including psychiatric symptoms, current and past medications or therapies
- Information from the memory testing

- Information on changes in your psychiatric symptoms that occur over the testing period

Others who will have access to your information for this research project are the University's Institutional Review Board (the committee that oversees research studying people) and authorized members of the University of Utah workforce who need the information to perform their duties (for example: to provide treatment, to ensure integrity of the research, and for accounting or billing matters).

If we share your information with anyone outside the University of Utah Health Sciences you will not be identified by name, social security number, address, telephone number, or any other information that would directly identify you, unless required by law.

You may revoke this authorization. This must be done in writing. You must either give your revocation in person to the Principal Investigator or the Principal Investigator's staff, or mail it to: Dr. Howard Weeks 501 Chipeta Way, Salt Lake City, Utah 84108. If you revoke this authorization, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research. This authorization lasts until this study is finished.

Consent
I confirm that I have read and understand this consent and authorization document and have had the opportunity to ask questions. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. I will be given a signed copy of the consent and authorization form to keep.

I agree to participate in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

_____
Participant's Name

_____ _____
Participant's Signature Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

Consent and Authorization Document
Neurocognitive Effects of Bifrontal ECT Substudy

Background
You are being invited to take part in a research study conducted by researchers from the Departments of Psychiatry, Anesthesiology, Psychology and Neurology, University of Utah. Before you decide if you want to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you want to volunteer to take part in this study.

One of the standard medical treatments for moderate to severe clinical depression is Electroconvulsive Therapy (ECT), also known as "shock treatment". These ECT treatments are administered by physicians together with relaxant drugs and anesthetic medications and other therapeutic procedures as your physicians may in their judgment determine to be necessary or appropriate. ECT treatments are usually repeated at intervals, usually every 2-3 days for about 2.5 to 3.5 weeks and about 8 total treatments. In many cases, a series of ECT treatments leads to substantial improvement in symptoms of depression. We are investigating the memory effects of ECT. Your physician and the physicians involved in this study believe that you are an appropriate candidate for ECT.

Study Procedure:
You have been referred to have ECT based on the symptoms of your illness and your physician's clinical judgment. This study will in no way change the standard practice of ECT and the delivery of your treatments.

A series of memory and mental function tests will be performed prior to your 1st ECT and then be repeated 12-24 hours after the 8th treatment and 4 weeks after the 8th and final treatment. Changes in severity of depressive symptoms will be assessed by a clinical interview before each of the 8 treatment sessions, as well as 12-24 hours after the last treatment session and at 4 weeks after the last treatment session. Each set of testing will take approximately 1.5 hours.

Risks: The memory testing procedures involve minimal risk to participants. You may become frustrated with the testing. If you feel upset from this experience, you can tell the researcher, and they will tell you about resources available to help.

Benefits: You will not receive any direct benefits from participating. However, if we find that there is no significant memory impairment with bifrontal ECT, this may be very helpful in the future to patients considering treatment with ECT. The information may also provide clues to the best memory sparing method of performing ECT, which may assist researchers in developing new treatments.

Alternative Procedures
If you do not want to take part in the study, you may choose to not participate in this study. This will in no way affect the treatment you receive from your medical providers.

Confidentiality
We will keep all research records that identify you private to the extent allowed by law. Records about you will be kept locked in filing cabinets or on computers protected with passwords. Only those who work with this study will be allowed access to your information. However, representatives from the Food and Drug Administration may

inspect and/or copy the records that identify you. Results of the study may be published; however, your name and other identifying information will be kept private.

Person to Contact
If you have questions, complaints or concerns about this study, or if you think you may have been injured from being in this study, you can contact Dr. Howard Weeks at 801-583-2500. Dr. Weeks can be reached at this number 24 hours a day.

Institutional Review Board
Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

Voluntary Participation
It is up to you to decide whether or not to take part in this research. If you do decide to take part you will be asked to sign this consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the relationship you have with the investigator or staff nor standard of care you receive.

Costs to Participants and Compensation
There are no costs to you or any compensation for any of the procedures described above. However, if you are assigned to the conventional ECT treatment, and you have medical insurance coverage, we will bill your provider for these treatment costs in the ordinary manner.

Authorization for Use of Your Protected Health Information
Signing this document means you allow us, the researchers in this study, and others working with us to use information about your health for this research study. You can choose whether or not you will participate in this research study. However, in order to participate you have to sign this consent and authorization form.

This is the information we will use:

- Name, address, and telephone number
- Medical history including psychiatric symptoms, current and past medications or therapies
- Information from the memory testing
- Information on changes in your psychiatric symptoms that occur over the testing period

Others who will have access to your information for this research project are the University's Institutional Review Board (the committee that oversees research studying people) and authorized members of the University of Utah workforce who need the information to perform their duties (for example: to provide treatment, to ensure integrity of the research, and for accounting or billing matters).

If we share your information with anyone outside the University of Utah Health Sciences you will not be identified by name, social security number, address, telephone number, or any other information that would directly identify you, unless required by law.

You may revoke this authorization. This must be done in writing. You must either give your revocation in person to the Principal Investigator or the Principal Investigator's staff, or mail it to: Dr. Howard Weeks 501 Chipeta Way, Salt Lake City, Utah 84108. If you revoke this authorization, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research. This authorization lasts until this study is finished.

Consent
I confirm that I have read and understand this consent and authorization document and have had the opportunity to ask questions. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. I will be given a signed copy of the consent and authorization form to keep.

I agree to participate in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

_____
Participant's Name

_____ _____
Participant's Signature Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

APPENDIX B

SUBJECTIVE QUESTIONS

Subject #: Pre Post Follow-up Date:

On a scale of 1 to 7, with a rating of 1 reflecting no memory problems at all and 7 indicating major or severe difficulties with memory, where would you rate your memory over the past 24 hours? (circle your response)

1 2 3 4 5 6 7

Comments:

Subject #: Follow-up Only Date:

On a scale of 1 to 7, please rate how effective you feel your treatment was with 1 being completely ineffective and 7 being extremely effective? (circle your response)

1 2 3 4 5 6 7

Comments:

REFERENCES

American Psychiatric Association. (2010). Practice guideline for the treatment of patients with major depressive disorder (3rd Ed.) American Psychiatric Association: Arlington, VA.

Bailine, S., Rifkin, A., Kayne, E., Selzer, J., Vital-Herne, J., Blieka, M., et al. (2000). A comparison of bifrontal and bitemporal ECT for major depression. *American Journal of Psychiatry, 157*(1), 121-123.

Bakewell, C.J., Russo, J., Tanner, C., Avery, D., & Neumaier, J.F. (2004). Comparison of clinical efficacy and side effects for bitemporal and bifrontal electrode placement in electroconvulsive therapy. *Journal of ECT, 20*(3), 145-153.

Benedict, R.H.B., Schretlen, D., Groninger, L., & Brandt, J. (1998). The Hopkins verbal learning test - revised: Normative data and analysis of interform and test-retest reliability. *Clinical Neuropsychologist, 12*(1), 43-55.

Brandt, J., & Benedict, R.H.B. (2001). Hopkins Verbal Learning Test-Revised Professional Manual. Lutz, FL: Psychological Assessment Resources.

Calev, A., Gaudino, E.A., Squires, N.K., Zervas, I.M., & Fink, M. (1995). ECT and non-memory cognition: A review. *British Journal of Clinical Psychology, 34*, 505-515.

Crowley, K., Pickle, J., Dale, R., & Fattal, O. (2008). A critical examination of bifrontal electroconvulsive therapy: Clinical efficacy, cognitive side effects, and directions for future research. *Journal of Electroconvulsive Therapy, 24*(4), 268-271.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001a). Delis-Kaplan Executive Function System (DKEFS): Examiner's Manual. San Antonio, TX: The Psychological Corporation.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001b). Delis-Kaplan Executive Function System (DKEFS): Technical Manual. San Antonio, TX: The Psychological Corporation.

Englehardt, W., Carl, G., & Hartung, E. (1993). Intra-individual open comparison of burst-suppression-Isoflurane-anaesthesia versus electroconvulsive therapy in the treatment of severe depression. *European Journal of Anaesthesiology, 10*, 113-118.

Eschweiler, G.W., Vonthein, R., Bode, R., Huell, M., Conca, A., Peters, O., et al. (2007). Clinical efficacy and cognitive side effects of bifrontal versus Right unilateral electroconvulsive therapy (ECT): A short-term randomised controlled trial in pharmaco-resistant major depression. *Journal of Affective Disorder, 101*, 149-157.

Fink, M., & Taylor, M.A. (2007). Electroconvulsive therapy: Evidence and challenges. *JAMA, 298*(3), 330-331.

Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189-198.

Grunhaus, L., Hirschman, S., Dolberg, O., Schreiber, S., & Dannon, P. (2001). Coadministration of melatonin and fluoxetine does not improve the 3-month outcome following ECT. *The Journal of ECT, 17*(2), 124-128.

Hamilton, M. (1967). Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology, 6*, 278-296.

Heikman, P., Kalska, H., Katila, H., Sarna, S., Tuunainen, A., & Kuoppasalmi, K. (2002). Right unilateral and bifrontal electroconvulsive therapy in the treatment of depression: A preliminary study. *Journal of ECT, 18*(1), 26-30.

Hermann, R., Dorwart, R., Hoover, C., & Brody, J. (1995). Variation in ECT use in the United States. *American Journal of Psychiatry, 152*, 869-875.

Inglis, J. (1969). Electrode placement and the effect of E.C.T. on mood and memory in depression. *Canadian Psychiatric Association Journal, 14,* 463-471.

Kellner, C.H., Knapp, R., Husain, M.M., Rasmussen, K., Sampson, S., Cullum, M. et al. (2010). Bifrontal, bilateral, and Right unilateral electrode placement in ECT: randomized trial. *British Journal of Psychiatry, 196*, 226-234.

Kellner, C.H., Knapp, R., Petrides, G., Rummans, T., Husain, M.M., Rasmussen, K. (2006). Continuation ECT vs pharmacotherapy for relapse prevention in major depression. *Archives of General Psychiatry, 63*(12), 1337-1344.

Kessler R.C., Chiu, W.T., Demler, O. &, Walters, E.E. (2005). Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Archives of General Psychiatry*, *62*(6), 617-27.

Kho, K., van Vreeswijk, M.F., Simpson, S., & Zwinderman, A.H. (2003). A meta-analysis of electroconvulsive therapy efficacy in depression. *Journal of ECT, 19*(3), 139-147.

Langer, G., Karazman, R., Neumark, J., Saletu, B., Schonbeck, G., Grunberger, J., et al. (1995). Isoflurane narcotherapy in depressive patients refractory to conventional antidepressant drug treatment. *Neuropsychobiology, 31*, 182-194.

Langer, G., Neumark, G., Koinig, M., Graf, M., & Schonbeck, G. (1985). Rapid psychotherapeutic effects of anesthesia with Isoflurane (ES narcotherapy) in treatment-refractory depressed patients. *Neuropsychobiology, 14*, 118-120.

Lawson, J.S., Inglis, J., Delva, N.J., Rodenburg, J., Waldron, J.J., & Letemendia, F.J. (1990). Electrode placement in ECT: Cognitive effects. *Psychological Medicine, 20*, 335-344.

Letemendia, F.J., Delva, N.J., Rodenburg, M., Lawson, J.S., Inglis, J., Waldron, J.J., et al. (1993). Therapeutic advantage of bifrontal electrode placement in ECT. *Psychological Medicine, 23*, 349-60.

Lisanby, S. (2007). Electroconvulsive therapy for depression. *New England Journal of Medicine, 357*(19), 1939-1945.

Malcolm, K. (1989). Patients' perceptions and knowledge of electroconvulsive therapy. *Psychiatric Bulletin, 13*,161-165.

McElhiney, M., Moody, B., & Sackeim, H. (1997). The Autobiographical Memory Interview - Short Form. New York: New York State Psychiatric Institute.

McElhiney, M., Moody, B., Steif, B., Prudic, J., Debanand, D., Nobler, M., et al. (1995). Autobiographical memory and mood: Effects of electroconvulsive therapy. *Neuropsychology, 9*(4), 501-517.

Prudic, J., Olfson, M., Marcus, S., Fuller, R., & Sackeim, H. (2004). Effectiveness of electroconvulsive therapy in community settings. *Biological Psychiatry, 55*, 301-312.

Prudic, J., Olfson, M., & Sackeim, H. (2001). Electro-convulsive therapy practices in the community. *Psychological Medicine, 31*, 929-934

Ranjkesh, F., Barekatain, M., & Akuchakian, S. (2005). Bifrontal versus right unilateral and bitemporal electroconvulsive therapy in major depressive disorder. *Journal of ECT, 21*(4), 207-210.

Rose, D., Wykes, T., Leese, M., Bindman, J., & Fleischman, P. (2003). Patients' perspectives on electroconvulsive therapy: Systematic review. *British Medical Journal, 326*, 1363-1368.

Rush, A.J., Trivedi, M.H., Wisniewski S.R., Nierenberg A., Stewart J.W., Warden D., et al. (2006). Acute and longer term outcomes in depressed patients who require one or several treatment steps: A STAR*D report. *American Journal of Psychiatry, 163*(11), 1905-1917.

Sackeim, H., Haskett, R., Mulsant, B., Thase, M., Mann, J., Pettinati, H. et al. (2001). Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy. *Journal of the American Medical Association, 285*(10), 1299-1307.

Sackeim, H., Prudic, J., Devanand, D., Kiersky, J., Fitzsimmons, L., Moody, B., et al. (1993). Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *New England Journal of Medicine, 328*(12), 839-846.

Sackeim, H., Prudic, J., Fuller, R., Keilp, J., Lavori, P., & Olfson, M. (2007). The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology, 32*, 244-254.

Sackeim, H., Prudic, J., Nobler, M., Fitzsimmons, L., Lisanby, S., Payne, N. (2009). Effects of pulse width and electrode placements on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimulation, 1*(2), 71-83.

Schulze-Rauschenbach, S.A., Harms, U., Shclaepfer, T.E., Maier, W., Flakai, P., & Wagner, M. (2005). Distinctive neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression. *British Journal of Psychiatry, 186*, 410-416.

Shapiro, A.M., Benedict, R.H.B., Schretlen, D., & Brandt, J. (1999). Construct and concurrent validity of the Hopkins verbal learning test-revised. *Clinical Neuropsychologist, 13*(3), 348-358.

Squire, L.R., & Slater, P.C. (1983). Electroconvulsive therapy and complaints of memory dysfunction: A prospective three-year follow-up study. *British Journal of Psychiatry, 142*, 1-8.

Suchy, Y., Derbidge, C., & Cope, C. (2005). Behavioral Dyscontrol Scale-Electronic Version: First examination of reliability, validity, and incremental utility. *The Clinical Neuropsychologist, 19*, 4-26.

UK ECT Review Group. (2003). Efficacy and safety of electroconvulsive therapy in depressive disorders: A systematic review and meta-analysis. *The Lancet, 361*, 799-808.

Wechsler, D. (1997). Wechsler Adult Intelligence Scale (3rd ed.). San Antonio, TX: Psychological Corporation.

Wechsler, D. (1997). Wechsler Memory Scale (3rd ed.). San Antonio, TX: Psychological Corporation.

Wechsler, D. (2001). Wechsler Test of Adult Reading. San Antonio, TX: Psychological Corporation.